```
=> d his full

     (FILE 'HOME' ENTERED AT 11:58:39 ON 07 FEB 2003)

     FILE 'REGISTRY' ENTERED AT 11:59:04 ON 07 FEB 2003
                E DEXAMETHASONE/CN
L1            1 SEA ABB=ON  DEXAMETHASONE/CN
                D
L2         1130 SEA ABB=ON  C13H15N3O3/MF
L3          815 SEA ABB=ON  L2 AND NR=2 AND LRS=2
                E 6-THIOGUANINE/CN
L4            1 SEA ABB=ON  6-THIOGUANINE/CN
                D
                D RN
                E ACRIFLAVINIUM HCL/CN
L5            1 SEA ABB=ON  "ACRIFLAVINIUM CHLORIDE"/CN
                D
                E ACRIFLAVINIUM/CN
                E ACRIFLAVINE
                E ACRIFLAVINE/CN
L6            1 SEA ABB=ON  ACRIFLAVINE/CN
                D
L7            1 SEA ABB=ON  C14H11CLN3/MF
                D
L8          417 SEA ABB=ON  C14H11N3/MF
L9           43 SEA ABB=ON  L8 AND NR=3 AND NRS=1
                D SCAN
L10             STR
L11           0 SEA SSS SAM L10
L12           0 SEA SSS FUL L10
                D COST
L13           0 SEA SSS SAM L10
L14             STR L0
L15           0 SEA SSS SAM L14
L16           0 SEA SSS FUL L14
L17             STR L14
L18           0 SEA SSS SAM L17
L19           0 SEA SSS FUL L17
                D COST
                D L18
L20             STR L17
L21           0 SEA SSS SAM L20
L22             STR L20
L23           0 SEA SSS SAM L22
L*** DEL        STR L20
L24             STR L22
L25          11 SEA SSS SAM L24
                D SCAN
L26         367 SEA SSS FUL L24
                D L17
L27           0 SEA SUB=L26 SSS SAM L17
L28             STR L20
L29          20 SEA SUB=L26 SSS SAM L28
L30             STR L28
L31           0 SEA SSS SAM L30
L32           0 SEA SUB=L26 SSS SAM L30
L33          54 SEA SUB=L26 SSS FUL L30
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L34           1 SEA ABB=ON  86-40-8/RN
L35        1130 SEA ABB=ON  C13H15N3O3/MF
L36           0 SEA ABB=ON  CN4/ES
L37           0 SEA ABB=ON  CN4/ELS
L38           1 SEA ABB=ON  BENZYLIDENE/CN
L39           1 SEA ABB=ON  HYDRAZINE/CN
L40           1 SEA ABB=ON  TETRAZOLE/CN
L41       42537 SEA ABB=ON  16.525.8/RID
L42           0 SEA ABB=ON  L35 AND 16.525.8/RID
L43         259 SEA ABB=ON  L35 AND NR=2 AND NRS=1
L44         556 SEA ABB=ON  L35 AND NR=2 AND NRS=2
L45           0 SEA ABB=ON  L44 AND CN4/ELS
L46           0 SEA ABB=ON  L44 AND 16.525.8/RID
L47           1 SEA ABB=ON  DEXAMETHASONE/CN
L48          62 SEA ABB=ON  L2 AND 46.156.30/RID
L49           1 SEA ABB=ON  10444-59-4/RN
L50           1 SEA ABB=ON  43180-35-4/RN
L51           1 SEA ABB=ON  1990-01-8/RN
L52           1 SEA ABB=ON  50-02-2/RN
L53           1 SEA ABB=ON  154-42-7/RN
L54           1 SEA ABB=ON  86-40-8/RN
L55           6 SEA ABB=ON  L49 OR L50 OR L51 OR L52 OR L53 OR L54 see attached
                            structures & compds searched

FILE 'HCAPLUS' ENTERED AT 14:53:36 ON 07 FEB 2003
L56       31538 SEA ABB=ON  L55 OR (?GLAUCARUBOLONE? OR ?DEXAMETHASONE? OR
                            6(W)?THIOGUANINE? OR ?ACRIFLAVINIUM(W)(HYDROCHLORIDE OR HCL?))
L57         177 SEA ABB=ON  L56 AND (?PARATHYROID?(W)?HORMONE?(W)?RELATED?(W)?P
                            ROTEIN? OR ?PTHRP? OR (?CALCIUM? OR CA)(W)(?HOMEOSTAS? OR
                            ?HOMEOSTAT? OR ?REGULAT?) OR (?HYPER? OR ?HYPO?)(W)?CALCEM? OR
                            ?OSTEOPOR? OR ?OSTEOLYS? OR ?OSTEOLYT?)
L58          41 SEA ABB=ON  L56 AND (?PARATHYROID?(W)?HORMONE?(W)?RELATED?(W)?P
                            ROTEIN? OR ?PTHRP?)
L59           5 SEA ABB=ON  L58 AND ((?CALCIUM? OR CA)(W)(?HOMEOSTAS? OR
                            ?HOMEOSTAT? OR ?REGULAT?) OR (?HYPER? OR ?HYPO?)(W)?CALCEM? OR
                            ?OSTEOPOR? OR ?OSTEOLYS? OR ?OSTEOLYT?)
L60        2328 SEA ABB=ON  L56 AND (?CALCI? OR CA OR ?CALCE? OR ?OSTEO?)
L61           0 SEA ABB=ON  L58 AND (?CALCIUM? OR CA)(W)?HOMEOSTAS?
L62           0 SEA ABB=ON  L58 AND (?CALCIUM? OR CA)(3A)?HOMEOSTAS?
L63          14 SEA ABB=ON  L56 AND (CA OR ?CALCIUM?)(W)(?REGULAT?)
L64         849 SEA ABB=ON  L56 AND ?OSTEO?
L65          10 SEA ABB=ON  L56 AND (?OSTEOLY?)
L66          27 SEA ABB=ON  L59 OR L63 OR L65
L67          63 SEA ABB=ON  L58 OR L66
L68       21265 SEA ABB=ON  L55
L69         121 SEA ABB=ON  L68 AND (?PARATHYROID?(W)?HORMONE?(W)?RELATED?(W)?P
                            ROTEIN? OR ?PTHRP? OR (?CALCIUM? OR CA)(W)(?HOMEOSTAS? OR
                            ?HOMEOSTAT? OR ?REGULAT?) OR (?HYPER? OR ?HYPO?)(W)?CALCEM? OR
                            ?OSTEOPOR? OR ?OSTEOLYS? OR ?OSTEOLYT?)
L70          27 SEA ABB=ON  L68(L)(?PARATHYROID?(W)?HORMONE?(W)?RELATED?(W)?PRO
                            TEIN? OR ?PTHRP? OR (?CALCIUM? OR CA)(W)(?HOMEOSTAS? OR
                            ?HOMEOSTAT? OR ?REGULAT?) OR (?HYPER? OR ?HYPO?)(W)?CALCEM? OR
                            ?OSTEOPOR? OR ?OSTEOLYS? OR ?OSTEOLYT?) 27 cits, attached

FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO' ENTERED AT
15:21:54 ON 07 FEB 2003
L71           0 SEA ABB=ON  L70
L72         734 SEA ABB=ON  L69
```

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L73         132 SEA ABB=ON  L58
L74          93 SEA ABB=ON  L68 AND (?PARATHYROID?(W) ?HORMONE?(W) ?RELATED?(W)
                 ?PROTEIN? OR ?PTHRP?)
L75          58 DUP REMOV L74 (35 DUPLICATES REMOVED)
L76          39 SEA ABB=ON  L75 AND (CALCI? OR OSTEO?)
```

39 cits, attached

Because there were so many cits retrieved from these databases, I combined those with PTH+P with the Ca + osteo terms to limit the number.

If you need any further searching, please let me know.

=> d l55 1-6

L55 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN **43180-35-4** REGISTRY
CN Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, labeled with tritium, (11.beta.,16.beta.)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3H-Betamethasone
FS STEREOSEARCH
MF C22 H29 F O5
LC STN Files: CA, CAPLUS
IL XH-3

Absolute stereochemistry.

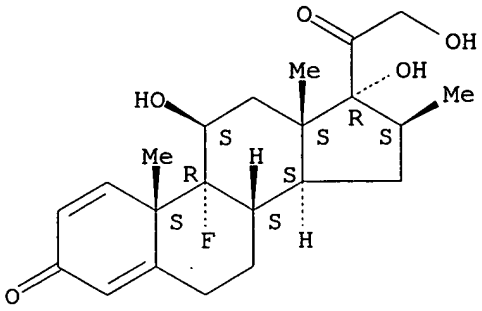

Fig 2

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L55 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN **10444-59-4** REGISTRY
CN Benzaldehyde, 1H-tetrazol-5-ylhydrazone (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzaldehyde, 1H-tetrazol-5-ylhydrazone (8CI)
CN Benzaldehyde, tetrazol-5-ylhydrazone (6CI, 7CI)
FS 3D CONCORD
DR 56332-35-5
MF C8 H8 N6
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

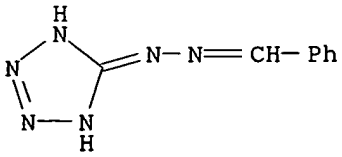

Fig 1

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1962 TO DATE)

15 REFERENCES IN FILE CAPLUS (1962 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L55 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN **1990-01-8** REGISTRY
CN Picras-3-ene-2,16-dione, 11,20-epoxy-1,11,12,15-tetrahydroxy-, (1.beta.,11.beta.,12.alpha.,15.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-1,11c-(Epoxymethano)phenanthro[10,1-bc]pyran, picras-3-ene-2,16-dione deriv.
CN 2H-1,11c.beta.-(Epoxymethano)phenanthro[10,1-bc]pyran-5,10(3H,6a.beta.H)-dione, 1,3a.beta.,4,7,7a.alpha.,11,11a,11b-octahydro-1.alpha.,2.alpha.,4.beta.,11.beta.-tetrahydroxy-3.alpha.,8,11a.beta.-trimethyl- (8CI)
CN Glaucarubolone (7CI)
OTHER NAMES:
CN (-)-Glaucarubolone
FS STEREOSEARCH
DR 4779-14-0
MF C20 H26 O8
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CHEMCATS, CHEMINFORMRX, DDFU, DRUGU, EMBASE, IPA, MEDLINE, NAPRALERT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.

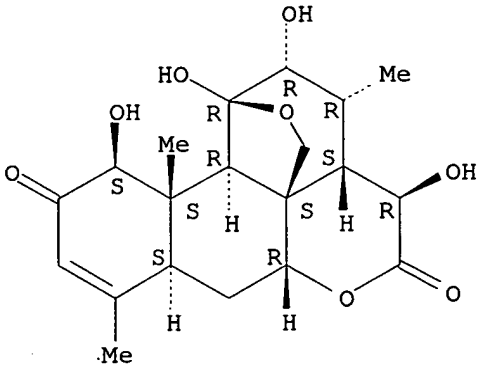

Fig 3

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

49 REFERENCES IN FILE CA (1962 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
49 REFERENCES IN FILE CAPLUS (1962 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L55 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN **154-42-7** REGISTRY
CN 6H-Purine-6-thione, 2-amino-1,7-dihydro- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Purine-6(1H)-thione, 2,3-dihydro-2-imino- (6CI)
CN Purine-6(1H)-thione, 2-amino- (7CI, 8CI)

CN Purine-6-thiol, 2-amino- (8CI)
OTHER NAMES:
CN 2-Amino-6-mercaptopurine
CN 2-Amino-9H-purine-6(1H)-thione
CN 2-Aminopurine-6-thiol
CN 6-Mercaptoguanine
CN 6-TG
CN 6-Thioguanine
CN Guanine, thio-
CN NSC 752
CN Tabloid
CN Thioguanine
CN Tioguanin
CN Tioguanine
FS 3D CONCORD
DR 611-67-6, 1125-65-1, 1832-72-0, 5632-51-9
MF C5 H5 N5 S
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

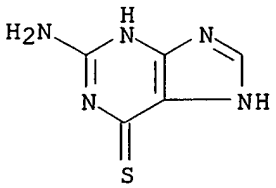

Fig 5

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1404 REFERENCES IN FILE CA (1962 TO DATE)
57 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1405 REFERENCES IN FILE CAPLUS (1962 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L55 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN **86-40-8** REGISTRY
CN Acridinium, 3,6-diamino-10-methyl-, chloride (8CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,6-Diamino-10-methylacridinium chloride (7CI)
OTHER NAMES:
CN 2,8-Diamino-10-methylacridinium chloride
CN 3,6-Diamino-N-methylacridinium chloride
CN Avlon
CN Burnol
CN C.I. 46000
CN Chromoflavine

MF C14 H14 N3 . Cl
CI COM
LC STN Files: AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, CIN, EMBASE, GMELIN*, MSDS-OHS, NIOSHTIC, PHARMASEARCH, PROMT, RTECS*, SPECINFO, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (837-73-0)

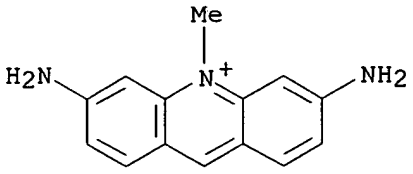

Fig 6

● Cl⁻

80 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
80 REFERENCES IN FILE CAPLUS (1962 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L55 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN **50-02-2** REGISTRY
CN Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11.beta.,16.alpha.)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Dehydro-16.alpha.-methyl-9.alpha.-fluorohydrocortisone
CN 16.alpha.-Methyl-9.alpha.-fluoro-.DELTA.1-hydrocortisone
CN 16.alpha.-Methyl-9.alpha.-fluoro-1,4-pregnadiene-11.beta.,17.alpha.,21-triol-3,20-dione
CN 16.alpha.-Methyl-9.alpha.-fluoro-11.beta.,17.alpha.,21-trihydroxypregna-1,4-diene-3,20-dione
CN 16.alpha.-Methyl-9.alpha.-fluoroprednisolone
CN 9-Fluoro-11.beta.,17,21-trihydroxy-16.alpha.-methylpregna-1,4-diene-3,20-dione
CN 9.alpha.-Fluoro-11.beta.,17.alpha.,21-trihydroxy-16.alpha.-methyl-1,4-pregnadiene-3,20-dione
CN 9.alpha.-Fluoro-16.alpha.-methyl-1,4-pregnadiene-11.beta.,17.alpha.,21-triol-3,20-dione
CN 9.alpha.-Fluoro-16.alpha.-methyl-11.beta.,17,21-trihydroxypregna-1,4-diene-3,20-dione
CN 9.alpha.-Fluoro-16.alpha.-methylprednisolone
CN Aeroseb-Dex
CN Aphtasolon
CN Aphthasolone
CN Azium
CN Calonat
CN Corsone

CN Cortisumman
CN Decacort
CN Decaderm
CN Decadron
CN Decalix
CN Decasone
CN Dectancyl
CN Dekacort
CN Deltafluorene
CN Dergramin
CN Deronil
CN Desadrene
CN Desameton
CN Deseronil
CN Dexa-Cortidelt
CN Dexa-Cortisyl
CN Dexa-Mamallet
CN Dexa-Scheroson
CN Dexa-sine
CN Dexacort
CN Dexacortal
CN Dexacortin
CN Dexadeltone
CN Dexafarma
CN Dexalona
CN Dexaltin
CN Dexameth
CN Dexamethasone
CN Dexamethasone alcohol
CN Dexamonozon
CN Dexapolcort
CN Dexapos
CN Dexaprol
CN Dexason
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS STEREOSEARCH
DR 8054-59-9, 137098-19-2
MF C22 H29 F O5
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.

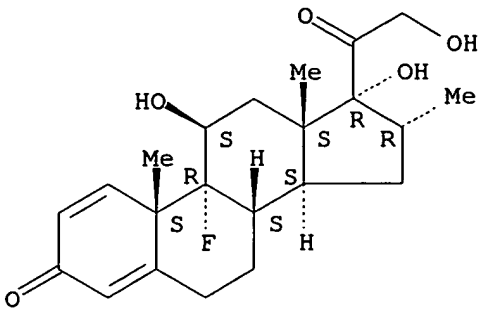

Fig 4

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

19683 REFERENCES IN FILE CA (1962 TO DATE)
256 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19698 REFERENCES IN FILE CAPLUS (1962 TO DATE)
186 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> d que stat l70
L49           1 SEA FILE=REGISTRY ABB=ON  10444-59-4/RN
L50           1 SEA FILE=REGISTRY ABB=ON  43180-35-4/RN
L51           1 SEA FILE=REGISTRY ABB=ON  1990-01-8/RN
L52           1 SEA FILE=REGISTRY ABB=ON  50-02-2/RN
L53           1 SEA FILE=REGISTRY ABB=ON  154-42-7/RN
L54           1 SEA FILE=REGISTRY ABB=ON  86-40-8/RN
L55           6 SEA FILE=REGISTRY ABB=ON  L49 OR L50 OR L51 OR L52 OR L53 OR
                L54
L68       21265 SEA FILE=HCAPLUS ABB=ON  L55
L70          27 SEA FILE=HCAPLUS ABB=ON  L68(L)(?PARATHYROID?(W)?HORMONE?(W)?RE
                LATED?(W)?PROTEIN? OR ?PTHRP? OR (?CALCIUM? OR CA)(W)(?HOMEOSTA
                S? OR ?HOMEOSTAT? OR ?REGULAT?) OR (?HYPER? OR ?HYPO?)(W)?CALCE
                M? OR ?OSTEOPOR? OR ?OSTEOLYS? OR ?OSTEOLYT?)

=> d ibib abs hitrn 1-27

L70  ANSWER 1 OF 27  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:730826  HCAPLUS
DOCUMENT NUMBER:          138:532
TITLE:                    Cyclic adenosine monophosphate/protein kinase A
                          mediates parathyroid hormone/parathyroid
                          hormone-related protein receptor regulation of
                          osteoclastogenesis and expression of RANKL and
                          osteoprotegerin mRNAs by marrow stromal cells
AUTHOR(S):                Kondo, Hisatomo; Guo, Jun; Bringhurst, F. Richard
CORPORATE SOURCE:         Endocrine Unit, Massachusetts General Hospital and
                          Harvard Medical School, Boston, MA, USA
SOURCE:                   Journal of Bone and Mineral Research (2002), 17(9),
                          1667-1679
                          CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER:                American Society for Bone and Mineral Research
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Parathyroid hormone (PTH) is a major regulator of osteoclast formation and
     activation, effects that are assocd. with reciprocal up- and
     down-regulation of RANKL and osteoprotegerin (OPG), resp. The roles of
     specific downstream signals generated by the activated PTH/PTH-related
     protein (PTHrP) receptor (PTH1R), such as cAMP/protein kinase A (cAMP/PKA)
     and phospholipase C/protein kinase C (PLC/PKC), in controlling RANKL and
     OPG expression and osteoclastogenesis remain uncertain.  In MS1
     conditionally transformed clonal murine marrow stromal cells, which
     support PTH-induced osteoclast formation from cocultured normal spleen
     cells, PTH(1-34) increased RANKL and macrophage colony-stimulating factor
     (M-CSF) mRNA expression and decreased that of OPG when present
     continuously for 7-20 days at 37.degree. in the presence of dexamethasone
     (Dex).  In cells precultured for 7 days and then treated with PTH(1-34),
     similar reciprocal regulation of RANKL and OPG occurred, maximally at 6-24
     h, that was of greater amplitude than the changes induced by chronic (7-10
     days) PTH exposure.  These acute effects of PTH(1-34) were mimicked by PKA
     stimulators (8-bromoadenosine [8Br]-cAMP or forskolin [FSK]), blocked by
     the PKA inhibitor Rp-cAMPs but unaffected by the PKC inhibitor GF109203X.
     Amino-truncated PTH(1-34) analogs PTH(5-34) and PTH(7-34) neither
     increased cAMP prodn. in MS1 cells nor regulated RANKL or OPG mRNA.
     Reciprocal RANKL/OPG mRNA regulation was induced in MS1 cells by PTH(3-34)
     but only at high concns. that also increased cAMP.  The highly
     PKA-selective PTH analog [Gly1,Arg19]human PTH(1-28) exerted effects
```

similar to PTH(1-34) on RANKL and OPG mRNAs and on osteoclast formation, both in MS1/spleen cell cocultures and in normal murine bone marrow cultures. The direct PKC stimulator 12-O-tetradecanoylphorbol-13-acetate (PMA) did not induce RANKL mRNA in MS1 cells, but it did up-regulate OPG mRNA and also antagonized osteoclast formation induced by PTH(1-34) in both MS1/spleen cocultures and normal bone marrow cultures. Thus, cAMP/PKA signaling via the PTH1R is the primary mechanism for controlling RANKL-dependent osteoclastogenesis, although direct PKC activation may neg. regulate this effect of PTH by inducing expression of OPG.

IT **50-02-2**, Dexamethasone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cAMP/PKA mediates PTH/**PTHrP** receptor regulation of osteoclastogenesis and expression of RANKL, osteoprotegerin and M-CSF mRNAs by marrow stromal cells in the presence of dexamethasone)

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:343947 HCAPLUS
DOCUMENT NUMBER: 137:76349
TITLE: Recovery from osteoporosis through skeletal growth: early bone mass acquisition has little effect on adult bone density
AUTHOR(S): Gafni, Rachel I.; McCarthy, Edward F.; Hatcher, Tracy; Meyers, Jodi L.; Inoue, Nozomu; Reddy, Chitra; Weise, Martina; Barnes, Kevin M.; Abad, Veronica; Baron, Effrey
CORPORATE SOURCE: Unit on Growth and Development, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA
SOURCE: FASEB Journal (2002), 16(7), 736-738, 10.1096/fj.01-0640fje
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It is often assumed that bone mineral accretion should be optimized throughout childhood to maximize peak bone mass. In contrast, the authors hypothesized that bone mineral acquisition early in life would have little or no effect on adult bone mass because many areas of the juvenile skeleton are replaced in toto through skeletal growth. To test this hypothesis, the authors induced osteoporosis by administering dexamethasone to 5-wk-old rabbits for 5 wk and then allowed them to recover for 16 wk. Tibial bone mineral d. (ash wt./vol.) was decreased in the dexamethasone-treated animals at the end of treatment but recovered completely. Bone structure in the femur was assessed by histomorphometry. Trabecular and cortical bone in the distal metaphysis was made osteoporotic by dexamethasone, but was then replaced through endochondral bone formation and recovered. Periosteal bone formation rate in the diaphysis was decreased during dexamethasone treatment but afterwards rebounded above controls and normalized cortical width. The authors' data suggest that bone mineral acquisition early in life has little effect on adult bone d. because the juvenile bone is largely replaced through growth. If this concept generalizes, then interventions to maximize peak bone mass should be directed at adolescents rather than young children.

IT **50-02-2**, Dexamethasone

RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(bone mineral acquisition early in life effect on adult bone d. in relation to juvenile bone replacement through growth as studied in dexamethasone-induced **osteoporotic** model)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:225242 HCAPLUS
DOCUMENT NUMBER: 136:350794
TITLE: Leptin mediates the parathyroid hormone-related protein paracrine stimulation of fetal lung maturation
AUTHOR(S): Torday, J. S.; Sun, H.; Wang, L.; Torres, E.
CORPORATE SOURCE: Department of Pediatrics and Obstetrics and Gynecology, Harbor-University of California Los Angeles Research and Education Institute, Torrance, CA, 90502, USA
SOURCE: American Journal of Physiology (2002), 282(3, Pt. 1), L405-L410
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Developing rat lung lipo-fibroblasts express leptin beginning on embryonic day (E) 17, increasing 7- to 10-fold by E20. Leptin and its receptor are expressed mutually exclusively by fetal lung fibroblasts and type II cells, suggesting a paracrine signaling "loop.". This hypothesized mechanism is supported by the following exptl. data: (1) leptin stimulates the de novo synthesis of surfactant phospholipid by both fetal rat type II cells (400% - 100 ng/mL/24 h) and adult human airway epithelial cells (85% - 100 ng/24 h); (2) leptin is secreted by lipofibroblasts in amts. that stimulate type II cell surfactant phospholipid synthesis in vitro; (3) epithelial cell secretions such as parathyroid hormone-related protein (PTHrP), PGE2, and dexamethasone stimulate leptin expression by fetal rat lung fibroblasts; (4) PTHrP or leptin stimulate the de novo synthesis of surfactant phospholipid (2- to 2.5-fold/24 h) and the expression of surfactant protein B (SP-B; >25-fold/24 h) by fetal rat lung explants, an effect that is blocked by a leptin antibody; and (5) a PTHrP receptor antagonist inhibits the expression of leptin mRNA by explants but does not inhibit leptin stimulation of surfactant phospholipid or SP-B expression, indicating that PTHrP paracrine stimulation of type II cell maturation requires leptin expression by lipofibroblasts. This is the first demonstration of a paracrine loop that functionally cooperates to induce alveolar acinar lung development.
IT **50-02-2**, Dexamethasone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(leptin mediates **parathyroid hormone-related protein** paracrine stimulation of fetal lung maturation)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:136264 HCAPLUS
DOCUMENT NUMBER: 135:162642
TITLE: High concentrations of dexamethasone suppress the proliferation but not the differentiation or further

maturation of human osteoblast precursors in vitro: Relevance to glucocorticoid-induced osteoporosis

AUTHOR(S): Walsh, S.; Jordan, G. R.; Jefferiss, C.; Stewart, K.; Beresford, J. N.

CORPORATE SOURCE: Bone Research Group, Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, UK

SOURCE: Rheumatology (Oxford) (2001), 40(1), 74-83
CODEN: RUMAFK; ISSN: 1462-0324

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The use of glucocorticoids (GCs) in the treatment of RA is a frequent cause of bone loss. In vitro, however, this same class of steroids has been shown to promote the recruitment and/or maturation of primitive osteogenic precursors present in the colony forming unit-fibroblastic (CFU-F) fraction of human bone and marrow. In an effort to reconcile these conflicting observations, we investigated the effects of the synthetic GC dexamethasone (Dx) on parameters of growth and osteogenic differentiation in cultures of bone marrow stromal cells derived from a large cohort of adult human donors (n = 30). Marrow suspensions were cultured in the absence and presence of Dx at concns. between 10 pM and 1 .mu.M. After 28 days we detd. the no. and diam. of colonies formed, the total no. of cells, the surface expression of receptors for selected growth factors and extracellular matrix proteins and, based on the expression of the developmental markers alk. phosphatase (AP) and the antigen recognized by the STRO-1 monoclonal antibody, the proportion of cells undergoing osteogenic differentiation and their extent of maturation. At a physiol. equiv. concn., Dx had no effect on the adhesion of CFU-F or on their subsequent proliferation, but did promote their osteogenic differentiation and further maturation. These effects were independent of changes in the expression of the receptors for fibroblast growth factors, insulin-like growth factor 1, nerve growth factor, platelet-derived growth factors and parathyroid hormone/parathyroid hormone-related protein, but were assocd. with changes in the no. of cells expressing the .alpha.2 and .alpha.4, but not .beta.1, integrin subunits. At supraphysiol. concns., the effects of Dx on the osteogenic recruitment and maturation of CFU-F and their progeny were maintained but at the expense of a decrease in cell no. A decrease in the proliferation of osteogenic precursors, but not in their differentiation or maturation, is likely to be a key factor in the genesis of GC-induced bone loss.

IT **50-02-2**, Dexamethasone
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high concns. of dexamethasone suppress proliferation but not differentiation or further maturation of human osteoblast precursors in vitro and relevance to glucocorticoid-induced **osteoporosis**)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:615882 HCAPLUS

DOCUMENT NUMBER: 131:317953

TITLE: Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis

AUTHOR(S): Hofbauer, Lorenz C.; Gori, Francesca; Riggs, B. Lawrence; Lacey, David L.; Dunstan, Colin R.;

Spelsberg, Thomas C.; Khosla, Sundeep
CORPORATE SOURCE: Endocrine Research Unit, Mayo Clinic and Mayo Foundation, Rochester, MN, 55905, USA
SOURCE: Endocrinology (1999), 140(10), 4382-4389
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Osteoporosis is a serious complication of systemic glucocorticoid use. However, while glucocorticoids increase bone resorption in vitro and in vivo, the mechanism(s) of this effect are at present unclear. Recent studies have identified the osteoprotegerin (OPG) ligand (OPG-L) as the final effector of osteoclastogenesis, an action that is opposed by the sol. neutralizing receptor, OPG. Thus, we assessed glucocorticoid regulation of OPG and OPG-L in various human osteoblastic lineage cells using Northern anal., RT-PCR, and ELISA. Dexamethasone inhibited constitutive OPG mRNA (mRNA) steady-state levels by 70-90% in primary (MS) and immortalized stromal cells (hMS), primary trabecular osteoblasts (hOB), immortalized fetal osteoblasts (hFOB), and osteosarcoma cells (MG-63). In hFOB cells, dexamethasone inhibited constitutive OPG mRNA steady-state levels in a dose- and time-dependent fashion by 90%, and also suppressed cytokine-stimulated OPG mRNA steady-state levels. Dexamethasone-induced inhibition of OPG mRNA levels was not affected by the protein synthesis inhibitor, cycloheximide, and was shown to be due to inhibition of OPG gene transcription using a nuclear run-on assay. Moreover, dexamethasone also dose dependently (1010 M-10-7 M) inhibited constitutive OPG protein concns. in the conditioned medium of hFOB cells from 2.59.+-.0.02 ng/mL (control) to 0.30.+-.0.01 ng/mL (88% inhibition; $P < 0.001$ by ANOVA). Concurrently, dexamethasone stimulated OPG-L mRNA steady-state levels in MS and hFOB cells by 2- and 4-fold, resp. Treatment of murine marrow cultures with conditioned medium harvested from dexamethasone-treated MG-63 cells increased tartrate-resistant acid phosphatase (TRAP) activity by 54% ($P < 0.005$) compared with medium harvested from control-treated cells (in the presence of OPG-L and macrophage colony-stimulating factor). Moreover, dexamethasone (10-8 M) promoted osteoclast formation in vitro, as assessed by a 2.5-fold increase of TRAP activity in cell lysates ($P < 0.001$) and the appearance of TRAP-pos. multinucleated cells. Our data are thus consistent with the hypothesis that glucocorticoids promote osteoclastogenesis by inhibiting OPG and concurrently stimulating OPG-L prodn. by osteoblastic lineage cells, thereby enhancing bone resorption.

IT **50-02-2**, Dexamethasone
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin prodn. by glucocorticoids in human osteoblastic lineage cells and potential paracrine mechanisms of glucocorticoid-induced **osteoporosis**)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:581956 HCAPLUS
DOCUMENT NUMBER: 130:20524
TITLE: New drug screening using osteoblast clone cultivated by adult rat calvaria
AUTHOR(S): Deng, Li; Zheng, Hu; Weng, Lingling; Ide Hayao; Kiriu Mechiaki

CORPORATE SOURCE: School of Pharmacy, West China University of Medical Sciences, Chengdu, 610041, Peop. Rep. China
SOURCE: Huaxi Yaoxue Zazhi (1998), 13(2), 85-87
CODEN: HYZAE2; ISSN: 1006-0103
PUBLISHER: Huaxi Yike Daxue Yaoxueyuan
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Calvaria of adult female Wistar rat aged 25-35 wk were treated with F-12 culture contg. fetal bovine serum for 7 days, and then added with dexamethasone, 17.beta.-estradiol, or the new anti-osteoporosis drug XW630. The osteoblast bone formation was dynamically obsd. under a phase contrast microscope for 14-20 days. After Von Kossa staining, the bone nodule surface area was detd. by Bio multi scanner BMS-400 as the quant. index for statistical anal. Dexamethasone and XW630 had osteogenic promoting activity but estradiol did not. The results suggest that the method is valid in evaluation of the effect of osteogenic effect of tested drugs.

IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antiosteoporotic** drug screening using osteoblast clone cultivated by adult rat calvaria)

L70 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:426520 HCAPLUS
DOCUMENT NUMBER: 129:184395
TITLE: Antenatal corticosteroid therapy and risk of osteoporosis
AUTHOR(S): Ogueh, Onome; Khastgir, Gautam; Studd, John W. W.; Jones, Julia; Alaghband-Zadeh, Jamshid; Johnson, Mark Richard
CORPORATE SOURCE: Section of Obstetrics and Gynaecology, Imperial College School of Medicine at Chelsea and Westminster Hospital, London, SW109NH, UK
SOURCE: British Journal of Obstetrics and Gynaecology (1998), 105(5), 551-555
CODEN: BJOGAS; ISSN: 0306-5456
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study assessed the risk of maternal osteoporosis assocd. with antenatal corticosteroid administration for neonatal respiratory distress syndrome prophylaxis. Fourteen pregnant women who received dexamethasone therapy for fetal lung maturation in anticipation of delivery before 34 completed weeks of gestation were enrolled in a prospective longitudinal study at the maternity unit of Chelsea and Westminster Hospital, London. Blood samples were collected before dexamethasone administration, 24 h and 48 h after the course of dexamethasone, and within 24 h of delivery. Serum levels of carboxy terminal pro-peptide of type I pro-collagen (PICP) were measured to monitor the rate of bone formation, and serum levels of cross-linked carboxy terminal telopeptide (ICTP) were measured as a marker of bone resorption. Main outcome measures were changes in the markers of bone turnover following dexamethasone administration. Serum PICP levels dropped 24 h after dexamethasone therapy (P = 0.001), but partially recovered by 48 h (P = 0.014) to reach higher than pre-therapy levels at delivery (P = 0.044). Although there were no corresponding changes in the serum levels of ICTP after 24 and 48 h of therapy, levels increased from

pretherapy to delivery (P = 0.006). Antenatal corticosteroid therapy leads to a transient suppression of, followed by an increase in, bone formation without any significant alteration in the pattern of bone resorption expected during pregnancy.

IT **50-02-2**, Dexamethasone
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antenatal corticosteroid therapy and risk of **osteoporosis** in humans)

L70 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:227933 HCAPLUS
DOCUMENT NUMBER: 128:317376
TITLE: Regulation of the transcription of parathyroid-hormone/parathyroid-hormone-related peptide receptor mRNA by dexamethasone in ROS 17/2.8 osteosarcoma cells
AUTHOR(S): Yaghoobian, Jacqueline; Drueke, Tilman B.
CORPORATE SOURCE: INSERM Unite 90, Hopital Necker, Paris, Fr.
SOURCE: Nephrology, Dialysis, Transplantation (1998), 13(3), 580-586
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous studies have shown that dexamethasone enhanced the expression of parathyroid-hormone/parathyroid-hormone-related peptide (PTH/PTHrP) receptor mRNA in ROS 17/2.8 osteosarcoma cells. The aim of this study was to det. whether the induction of PTH/PTHrP receptor expression in such osteoblast-like cells is regulated at the gene level. Dexamethasone increased the steady-state levels of PTH/PTHrP receptor mRNA twofold at 6h, and nearly threefold at 24h. The half-life of the PTH/PTHrP receptor mRNA, in the presence of actinomycin D, was 6h both in untreated and in dexamethasone-treated cells. When measured by nuclear run-on assay, the rate of PTH/PTHrP receptor gene transcription was increased twofold at 24h. PTH/PTHrP receptor mRNA expression was blocked completely after 24h of treatment with cycloheximide. The binding of PTH/PTHrP to their receptor required the synthesis of new protein and was shown to be specifically dependent on the interaction of dexamethasone with the glucocorticoid receptor. These data indicate that the enhancing effect of dexamethasone on PTH/PTHrP receptor expression is rapid, required de novo protein synthesis, and increases the transcription rate of the PTH/PTHrP receptor gene.

IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dexamethasone regulation of PTH/**PTHrP** receptor mRNA transcription in osteoblast-like cell line)

L70 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:151231 HCAPLUS
DOCUMENT NUMBER: 128:214161
TITLE: Screening assay for identification of agents which alter expression of parathyroid hormone-related protein in mammalian cells
INVENTOR(S): Mundy, Gregory R.; Gallwitz, Wolfgang E.
PATENT ASSIGNEE(S): Osteoscreen, USA; Mundy, Gregory R.; Gallwitz, Wolfgang E.

SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807844	A2	19980226	WO 1997-US14836	19970822
WO 9807844	A3	19980827		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 5914233	A	19990622	US 1997-915868	19970821
AU 9741587	A1	19980306	AU 1997-41587	19970822
US 2002061509	A1	20020523	US 2001-879445	20010611

PRIORITY APPLN. INFO.:

US 1996-25215P	P	19960823
US 1997-915868	A	19970821
WO 1997-US14836	W	19970822
US 1999-283675	B3	19990401

AB A cell-based assay technique for identifying and evaluating chem. compds. and agents which affect the prodn. of parathyroid hormone-related protein (Pth-rP) in mammalian cells and other cell types is set forth. Specifically , tumor cell lines are transformed with an expression vector comprising a DNA sequence encoding a promoter region of PTH-rP operatively linked to a reporter gene encoding an assayable product and cultured under conditions which permit expression of the assayable product. Chem. agent and factors can then be identified by their ability to modulate the expression of the reporter gene, thereby affecting the prodn. of the assayable product. Such agents are then tested for inhibitory effects on tumor cell growth and for stimulatory effects on bone formation and repair. A chimeric gene comprising Pth-rP promoter linked to the firefly luciferase gene was prepd. This chimeric reporter gene was expressed in human breast cancer cell line MDA-MD-231 and human lung cancer cell line RWGT2. 6-Thioguanine and 5-benzylidene hydrazino-1,2,3,4-tetrazole were found to inhibit reporter gene expression. Both compds. lowered serum calcium and Pth-rP levels when administered to mice with squamous cell carcinoma of the lung. A similar assay indicated that acriflavinium hydrochloride stimulated expression of Pth-rP promoter-driven reporter genes.

IT **86-40-8 154-42-7**, 6-Thioguanine **10444-59-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(screening assay for identification of agents which alter expression of **parathyroid hormone-related protein** in mammalian cells)

L70 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:739247 HCAPLUS
DOCUMENT NUMBER: 128:33301
TITLE: Increases in osteocalcin after ovariectomy are

amplified by LPS injection: strain differences in bone remodeling
AUTHOR(S): Blanque, R.; Cottereaux, C.; Gardner, C. R.
CORPORATE SOURCE: CENTRE DE RECHERCHE ROUSSEL-UCLAF, ROMAINVILLE, 93235, Fr.
SOURCE: General Pharmacology (1998), 30(1), 51-56
CODEN: GEPHDP; ISSN: 0306-3623
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LPS (Escherichia coli serotype 0111:B4, 300 .mu.g/mouse IP) increases serum osteocalcin in normal female C57B16 mice from 2 to 6 h after its injection, with peak levels at 2-4 h after LPS. Both basal and LPS-stimulated serum osteocalcin were markedly inhibited by dexamethasone (10 mg/kg IP). When obsd. 3 h after LPS injection, serum osteocalcin was increased by ovariectomy (OVX) (with respect to sham-operated mice) and this increase was amplified in LPS-treated mice. This increase in osteocalcin was maximal 14 days after OVX, whereas urinary deoxypyridinoline cross-link levels were increased at all observation times (11-28 days). All these changes were also obsd. in Balb/c mice but their magnitudes were consistently lower than those in C57B16 mice. The authors propose that, (1) osteocalcin is a useful marker of bone remodeling in mice and the precision of measurement of changes in its levels after OVX is increased by LPS treatment and (2) C57B16 mice give greater magnitude and more consistent changes in both serum osteocalcin and urinary deoxypyridinoline cross-links after OVX, and may be a better strain for development of an in vivo model of post-menopausal osteoporosis.
IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(osteocalcin increase after ovariectomy amplification by bacterial lipopolysaccharide in mice inhibition by dexamethasone in relation to development of model for post-menopausal **osteoporosis**)

L70 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:325511 HCAPLUS
DOCUMENT NUMBER: 125:2219
TITLE: Influence of dexamethasone and 1,25-dihydroxyvitamin D on Walker carcinosarcoma 256 growth and parathyroid hormone-related protein secretion. Reply to comments
AUTHOR(S): Cohen-Solal, Martine; de Vernejoul, M. C.
CORPORATE SOURCE: ISER Unite 349, Hopital Laribaisiere, Paris, Fr.
SOURCE: Hormone and Metabolic Research (1996), 28(4), 210
CODEN: HMMRA2; ISSN: 0018-5043
PUBLISHER: Thieme
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A polemic in response to T. Schilling, R. Ziegler, and F. Rave (ibid. 209).
IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dexamethasone and dihydroxyvitamin D effect on Walker carcinosarcoma 256 growth and **parathyroid hormone-related protein** secretion)

L70 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:325510 HCAPLUS
DOCUMENT NUMBER: 125:2218
TITLE: Influence of dexamethasone and 1,25-dihydroxyvitamin D on Walker carcinosarcoma 256 growth and parathyroid hormone-related protein secretion. Comments
AUTHOR(S): Schilling, T.; Ziegler, R.; Raue, F.
CORPORATE SOURCE: Dep. Int. Med., Univ. Heidelberg, Keidelberg, Germany
SOURCE: Hormone and Metabolic Research (1996), 28(4), 209
CODEN: HMMRA2; ISSN: 0018-5043
PUBLISHER: Thieme
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A polemic in response to M. E. Cohen-Solal, et al. (ibid. 1995, 29(7), 403-7).
IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dexamethasone and dihydroxyvitamin D effect on Walker carcinosarcoma 256 growth and **parathyroid hormone-related protein** secretion)

L70 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:183354 HCAPLUS
DOCUMENT NUMBER: 124:252561
TITLE: Cell-specific and regulator-induced promoter usage and messenger ribonucleic acid splicing for parathyroid hormone-related protein
AUTHOR(S): Southby, Justine; Murphy, Leonie M.; Martin, T. John; Gillespie, Matthew T.
CORPORATE SOURCE: St. Vincent's Inst. Med. Res., Univ. Melbourne, Fitzroy, 3065, Australia
SOURCE: Endocrinology (1996), 137(4), 1349-57
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PTH-related protein (PTHrP) is the principle mediator of the syndrome of humoral hypercalcemia of malignancy and has potential paracrine actions on smooth muscle, epithelial cell growth, the placental calcium transport. The human PTHrP gene is complex: a combination of three promoters, one 5' alternative splicing event and alternative 3' splicing, which produces three PTHrP isoforms (139, 141, or 173 amino acids), results in multiple PTHrP mRNA (mRNA) species. We employed the RT-PCR technique to identify promoter usage and splicing patterns in a range of human cell lines. Cell line-specific utilization of the promoters and the 3' alternative splicing pathways was detected among bone, breast, kidney, and lung cell lines, although each cell line could potentially produce the three PTHrP isoforms. We also detd. whether some of the known regulators of PTHrP differentially modulate promoter usage or splicing patterns. Dexamethasone decreased the abundance of each of the alternative mRNA species. In contrast, epidermal growth factor and transforming growth factor-.beta. treatment increased the abundance of each PTHrP mRNA species, with particularly marked effects on promoter 1- and promoter 2-initiated transcripts, esp. those contg. exon VII or VIII. Epidermal growth factor treatment was found to alter PTHrP splicing patterns in a manner consistent with increased transcription from promoters 1 and 2 and stabilization of exon VII- and IX-contg. transcripts.
IT **50-02-2**, Dexamethasone

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(regulators of human gene **PTHrP** differentially modulate promoter usage or splicing patterns)

L70 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:916146 HCAPLUS
DOCUMENT NUMBER: 123:330753
TITLE: 1,25-Dihydroxyvitamin D and dexamethasone decrease in vivo Walker carcinoma growth, but not parathyroid hormone related protein secretion
AUTHOR(S): Cohen-Solal, M. E.; Bouizar, Z.; Denne, M. A.; Graulet, A. M.; Gueris, J.; Bracq, S.; Jullienne, A.; de Vernejoul, M. C.
CORPORATE SOURCE: Centre Viggo Petersen, Hopital Lariboisiere, Paris, Fr.
SOURCE: Hormone and Metabolic Research (1995), 27(9), 403-7
CODEN: HMMRA2; ISSN: 0018-5043
PUBLISHER: Thieme
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Parathyroid hormone related protein (PTHrP) is produced by several breast cancers. 1,25-Dihydroxyvitamin D (1,25[OH]2D) and dexamethasone (DEX) have been shown to decrease PTHrP mRNA expression in several cell lines. The authors therefore tested the in vivo effect of both steroids on PTHrP secretion and tumor development of the Walker carcinoma (WC). WC cells were injected s.c. in Fisher rats which were simultaneously treated with either vehicle, or 1,25(OH)2D (0.5 .mu.g/kg/d) or DEX (2 mg/kg/d). After 7 days, tumor wt. was significantly decreased in the 2 treated-groups as compared to the control group. Vehicle treated-rats developed hypercalcemia, which was also obsd. in rats treated with 1,25(OH)2D; by contrast, the plasma calcium was significantly decreased in the DEX-treated group compared to vehicle-treated rats. In a dose-effect expt., this dose of 1,25(OH)2D induced marked hypercalcemia in rats not implanted with WC, but was required to decrease the tumor wt. in implanted rats. In both 1,25(OH)2D and DEX-treated groups, plasma PTHrP levels were significantly decreased, but there was a similar correlation between PTHrP plasma level and tumor wt. in the three groups. Indeed, the cytosolic PTHrP content/mg tumor was identical in the 3 groups. By contrast, the PTHrP/actin mRNA in the tumor was significantly decreased in the 1,25(OH)2D group, comparatively to the vehicle and DEX groups. The results show that DEX and 1,25(OH)2D decrease WC tumor development in vivo, but do not change the PTHrP secretion by the remaining tumor although steady state PTHrP mRNA content level is decreased by 1,25(OH)2D.
IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 and dexamethasone decrease in vivo Walker carcinoma growth but not **parathyroid hormone related protein** secretion)

L70 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:868251 HCAPLUS
DOCUMENT NUMBER: 123:247313
TITLE: Amniotic fluid and plasma levels of parathyroid hormone-related protein and hormonal modulation of its secretion by amniotic fluid cells

AUTHOR(S): Dvir, Rina; Golander, Avraham; Jaccard, Niva; Yedwab, Gideon; Otremski, Itzhak; Spirer, Zvi; Weisman, Yosef
CORPORATE SOURCE: Bone Disease Unit, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel
SOURCE: European Journal of Endocrinology (1995), 133(3), 277-82
CODEN: EJOEEP; ISSN: 0804-4643
PUBLISHER: Scandinavian University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study, the authors demonstrated that the mean immunoreactive PTHrP concns. in amniotic fluid at mid-gestation (21.2 pmol/L) and at term (19.0 pmol/L) were 13-16-fold higher than levels measured in either fetal (1.6 pmol/L) or maternal plasma (1.4 pmol/L) at term and equal to levels found in plasma of patients with humoral hypercalcemia of malignancy. In vitro studied pointed to three possible sources of PTHrP in amniotic fluid: cultured amniotic fluid cells, cells derived from the amniotic membrane overlying the placenta and placental villous core mesenchymal cells. Treatment of cultured amniotic fluid cells with human prolactin, human placental lactogen (hPL) or human growth hormone (100 .mu.g/L) increased PTHrP secretion after 24 h by 43%, 109% and 90%, resp. Insulin-like growth factors I and II (100 .mu.g/L), insulin (100 .mu.g/L) and epidermal growth factor (EGF) (10 .mu.g/L) increased PTHrP secretion by 53%, 46%, 68% and 118%, resp. The stimulation of PTHrP secretion by EGF or by hPL was both time- and dose-dependent. In contrast, calcitriol and dexamethasone (10 nmol/L) decreased PTHrP secretion by 32% and 75%, resp. Estradiol, progesterone, dihydrotestosterone and human chorionic gonadotropin had no effect on PTHrP secretion. These findings support the notion that PTHrP may play a physiol. role in the uteroplacental unit and demonstrate that human amniotic fluid cells could be a useful model for studying the regulation of PTHrP prodn. and secretion by hormones and growth factors.

IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**PTHrP** of human amniotic fluid and blood plasma and **PTHrP** secretion by amniotic cells modulation by hormones)

L70 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:725446 HCAPLUS
DOCUMENT NUMBER: 123:133200
TITLE: Steroid regulation of parathyroid hormone-related protein expression and action in the rat uterus
AUTHOR(S): Paspaliaris, V.; Petersen, D. N.; Thiede, M. A.
CORPORATE SOURCE: Dep. Cardiovascular, Metabolic Disease, Pfizer Central Res., Groton, CT, 06340, USA
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (1995), 53(1-6), 259-65
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The gene encoding parathyroid hormone-related protein (PTHrP), an autocrine/paracrine inhibitor of vascular and nonvascular smooth muscle contractility, is regulated by hormonal steroids including estrogens (E2), 1,25-dihydroxyvitamin D3 (Vit D3) and glucocorticoids. While E2 increases PTHrP gene expression, Vit D3 and glucocorticoids inhibit transcriptional activity of this gene. In the uterus of ovariectomized rats, E2-treatment

increases both PTHrP mRNA levels and smooth muscle sensitivity to the action of PTHrP(1-34). To examine the action(s) of Vit D3 and glucocorticoids on these parameters, OVX rats were treated with E2, Vit D3 or the synthetic glucocorticoid, dexamethasone (Dex), alone, or with E2 following a 1 h pretreatment with Vit D3 or Dex. PTHrP and PTH/PTHrP receptor mRNA were measured by blot hybridization anal. of RNA prepd. from uteri collected 2, 4 and 24 h after treatment. Uterine horns were used to measure the effect of the steroids on the ability of PTHrP(1-34) to inhibit spontaneous myometrial contraction. When E2, Vit D3 and Dex were given alone, only E2 altered PTHrP mRNA levels in the uterus, however, a 1 h pretreatment with Dex but not Vit D3 markedly diminished this effect of E2. The temporal decline in uterine PTH/PTHrP receptor mRNA levels measured 2 and 4 h after E2 treatment inversely correlated to changes in sensitivity of the tissue to PTHrP(1-34) measured at 24 h after E2 administration. In comparison to E2 alone, treatment with Vit D3 and E2 augmented the uterine responsiveness to PTHrP(1-34) while pretreatment with Dex (1 mg/kg) and E2 decreased this response. These data indicate that in the uterus, Dex opposes the pos. effect of E2 on PTHrP gene activity and differentially modulates the action of PTHrP on myometrial tone. Moreover, elevations in the circulating levels of cortisol at term may serve to decrease both the uterine expression of PTHrP and the local action of PTHrP on the myometrium prior to parturition, therefore promoting myometrial contraction assocd. with labor.

IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(steroid regulation of **parathyroid hormone-related protein** expression and action in rat uterus)

L70 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:681407 HCAPLUS
DOCUMENT NUMBER: 123:102971
TITLE: Expression and secretion of parathyroid hormone-related protein by human bone-derived cells in vitro: Effects of glucocorticoids
AUTHOR(S): Walsh, C. A.; Birch, M. A.; Fraser, W. D.; Lawton, R.; Dorgan, J.; Walsh, S.; Sansom, D.; Beresford, J. N.; Gallagher, J. A.
CORPORATE SOURCE: Department Human Anatomy and Cell Biology, University, Liverpool, UK
SOURCE: Journal of Bone and Mineral Research (1995), 10(1), 17-55
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors investigated the prodn. of parathyroid hormone-related protein (PTHrP) by cells derived from explants of human bone. Using an immunoradiometric assay (IRMA), PTHrP was detected in conditioned medium from cultures of bone-derived cells from 6 of 7 patients investigated in this study. PTHrP mRNA was identified in human bone cells using reverse transcriptase-linked polymerase chain reaction (RT-PCR) and by Northern anal. Transcripts for PTHrP were detected in a purified population of alk. phosphatase pos. cells isolated from human bone marrow cultures by flow cytometry, confirming the expression of PTHrP mRNA by cells of the osteoblastic lineage. Prodn. of PTHrP was inhibited by 10-6 M of the glucocorticoids, prednisolone and desacetylated deflazacort, in a dose-dependent manner. In addn., RT-PCR followed by Southern blot anal.

detected a decrease in steady-state PTHrP mRNA in cultures of human bone-derived cells treated with 10-6 M prednisolone.

IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(glucocorticoid effect on **PTHrP** expression and secretion by human bone-derived cells in culture)

L70 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:544309 HCAPLUS
DOCUMENT NUMBER: 122:282520
TITLE: Dexamethasone treatment impairs calcium regulation and reduces bone mineralization in infant pigs
AUTHOR(S): Weiler, Hope A.; Wang, Zheng; Atkinson, Stephanie A.
CORPORATE SOURCE: Department of Pediatrics, McMaster University, Hamilton, ON, Can.
SOURCE: American Journal of Clinical Nutrition (1995), 61(4), 805-11
CODEN: AJCNAC; ISSN: 0002-9165
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Calcium and vitamin D metab., bone mineralization, and growth were studied in piglets randomly assigned to 15 d of dexamethasone (0.5 mg/kg/d, orally) or placebo. Growth velocity was significantly reduced by dexamethasone treatment. Pigs in the dexamethasone group demonstrated lower 45Ca absorption by in situ intestinal perfusion. Plasma 25-hydroxycholecalciferol (calcidiol) and 1,25-dihydroxycholecalciferol (calcitriol) were lower and the urinary ratio of calcium to creatinine was higher after 15 d of dexamethasone compared with placebo. Differences between pre- and postosteocalcin and pyridinoline were higher and wholebody, lumbar, and femur bone mineral d. were lower in dexamethasone-treated piglets. Dexamethasone-induced redns. in bone mineral mass likely result from reduced vitamin D status, reduced intestinal calcium absorption, elevated urinary calcium loss and direct effects of the steroid on bone. When dexamethasone is used in premature infants to improve lung function, neg. effects on growth and bone metab. could occur.

IT **50-02-2**, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dexamethasone impairment of **calcium regulation** and bone mineralization in infant)

L70 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:316070 HCAPLUS
DOCUMENT NUMBER: 120:316070
TITLE: Dexamethasone regulation of parathyroid hormone-related protein (PTHrP) expression in a squamous cancer cell line
AUTHOR(S): Glatz, Jane A.; Heath, Joan K.; Southby, Justine; O'Keeffe, Leonie M.; Kiriyama, Takeshi; Moseley, Jane M.; Martin, T. John; Gillespie, Matthew T.
CORPORATE SOURCE: The University of Melbourne Department of Medicine, St. Vincent's Hospital and St. Vincent's Institute of Medical Research, 41 Victoria Parade, Fitzroy, 3065, Victoria, Australia
SOURCE: Molecular and Cellular Endocrinology (1994), 101(1-2), 295-306

CODEN: MCEND6; ISSN: 0303-7207
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dexamethasone regulation of PTHrP expression has been studied in an epidermal squamous cancer cell line COLO 16, which secretes immunoreactive PTHrP into conditioned medium. Dexamethasone was found to suppress PTHrP expression in a time- and dose-dependent manner, which was reversible upon removal of dexamethasone. The half-maximal effective concn. of dexamethasone was 1 nM and an effect of dexamethasone on PTHrP mRNA was first obsd. after 2 h of treatment, with maximal inhibition by 6 h. Dexamethasone action on PTHrP expression was steroid-specific since progestin, 5.alpha.-dihydroxytestosterone and estrogen did not regulate PTHrP expression in COLO 16 cells. The gluocorticoid/progesterone receptor antagonist RU486 inhibited the dexamethasone effect, indicating glucocorticoid receptor-mediated regulation of PTHrP expression. The half-life of PTHrP mRNA in COLO 16 cells was approx. 120 min and was not altered by treatment of cells with dexamethasone. Nuclear run-on assays revealed that dexamethasone reduced PTHrP gene transcription in COLO 16 cells. Transient transfection assays with a series of reporter gene constructs encompassing 3.5 kb of the 5' end of the PTHrP gene failed to identify a region of the gene responsible for glucocorticoid down-regulation. PCR of reverse-transcribed RNA from COLO 16 cells revealed that dexamethasone down-regulated transcripts driven from all three promoters (i.e., the TATA promoters 5' to exons I and IV and the GC-rich promoter 5' to exon III) of the human PTHrP gene.
IT **50-02-2**, Dexamethasone
RL: BIOL (Biological study)
(**parathyroid hormone-related protein** expression in epidermal squamous cancer cell line COLO 16 regulation by)

L70 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:16485 HCAPLUS
DOCUMENT NUMBER: 118:16485
TITLE: Effect of some glucocorticoids on keratinocyte differentiation. I. Observation of transglutaminase activity in the calcium-regulated differentiation of cultured keratinocytes
AUTHOR(S): Mikami, Hideki; Mikami, Yukiko
CORPORATE SOURCE: Sch. Med., Hirosaki Univ., Hirosaki, 036, Japan
SOURCE: Nippon Hifuka Gakkai Zasshi (1992), 102(10), 1255-61
CODEN: NHKZAD; ISSN: 0021-499X
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The effects of glucocorticoids (GCs), i.e. hydrocortisone (HC), prednisolone (PR), triamcinolone acetonide (TA), and dexamethasone (DX), on epidermal cell keratinization were obsd. by using Ca-regulated differentiation of mouse epidermal cells in culture and by measuring the change of transglutaminase (TG) activity. HC, PR, TA lowered TG activity at <10-7 g/mL, whereas TG was activated at >10-8 g/mL. DX lowered TG activity at 10-4-10-8 g/mL. Apparently, the thinning of epidermal horny layer by topical GCs may be due to the direct inhibition of epidermal cell keratinization with high concn. of GCs. The order was HC, PR, TA and DX, at <10-7 g/mL, whereas it was DX, TA, HC and PR at >10-5 g/mL. From these results, the effect of GCs on epidermal cell keratinization depends on the kinds of added GCs, and the effect is not always parallel to the known antiphlogistic effect.
IT **50-02-2**, Dexamethasone

RL: BIOL (Biological study)
(**calcium-regulated** keratinocyte differentiation
response to, concn. in relation to)

L70 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:631106 HCAPLUS
DOCUMENT NUMBER: 111:231106
TITLE: Bone strength and fluoride supplementation
AUTHOR(S): Kanwar, K. C.; Dhar, Suman
CORPORATE SOURCE: Dep. Biophys., Panjab Univ., Chandigarh, 160014, India
SOURCE: Zoologische Jahrbuecher, Abteilung fuer Allgemeine Zoologie und Physiologie der Tiere (1989), 93(2), 145-8
CODEN: ZJZPAY; ISSN: 0044-5185
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Supplementation of rats (140-160 g) with fluoridated water (contg. 200 ppm F- vs. 1.5 ppm in untreated water) with or without Decadron (an adrenocorticosteroid prepn.) treatment for 6 wk increased the level of bone Ca and increased femur breaking strength. Application of Decadron only did not affect these parameters.
IT **50-02-2**, Decadron
RL: BIOL (Biological study)
(bone strength and calcium level response to fluoride supplementation and treatment with, **osteoporosis** in relation to)

L70 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:400790 HCAPLUS
DOCUMENT NUMBER: 109:790
TITLE: Studies on fluoride supplementation and experimental osteoporosis
AUTHOR(S): Kanwar, K. C.; Dhar, Suman
CORPORATE SOURCE: Dep. Biophys., Panjab Univ., Chandigarh, India
SOURCE: Research Bulletin of the Panjab University, Science (1987), 38(3-4), 127-31
CODEN: RBJUAT; ISSN: 0555-7631
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In rats, administration of NaF (200 ppm in the drinking water) and dexamethasone (400 .mu.g, twice a week, for 12 wk) increased the bone strength above that obsd. in rats treated with dexamethasone alone. Both dexamethasone and F- plus dexamethasone increased bone Ca2+. The results are discussed in relation to the treatment of osteoporosis by F-.
IT **50-02-2**, Dexamethasone
RL: BIOL (Biological study)
(**osteoporosis** response to, fluoride treatment in relation to)

L70 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:40621 HCAPLUS
DOCUMENT NUMBER: 102:40621
TITLE: 1,25-Dihydroxyvitamin D3 induction of CABP and stimulation of calcium uptake in embryonic chick duodena in culture: effects of verapamil and/or dexamethasone
AUTHOR(S): Corradino, Robert A.
CORPORATE SOURCE: New York State Coll. Vet. Med., Cornell Univ., Ithaca, NY, 14853, USA
SOURCE: Progress in Clinical and Biological Research (1984),

168(Epithelial Calcium Phosphate Transp.), 165-70
CODEN: PCBRD2; ISSN: 0361-7742
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Verapamil (10-6-10-4M) inhibited Ca-binding protein (CABP) formation and 45Ca uptake induced by 1,25-dihydroxyvitamin D3 (I) [32222-06-3] in embryonic chick duodenum in culture. These effects of verapamil were reversed by increasing the Ca concn. and by addn. of dexamethasone [**50-02-2**]. Evidently, **Ca regulates** the biosynthesis of CABP induced by I.

L70 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1984:605592 HCAPLUS
DOCUMENT NUMBER: 101:205592

TITLE: Calcium-45 uptake during the transition from reversible to irreversible liver injury induced by D-galactosamine in vivo

AUTHOR(S): Schiessel, Clemens; Forsthove, Claudia; Keppler, Dietrich
CORPORATE SOURCE: Biochem. Inst., Univ. Freiburg/Br., Freiburg, Fed. Rep. Ger.

SOURCE: Hepatology (Philadelphia, PA, United States) (1984), 4(5), 855-61
CODEN: HPTLD9; ISSN: 0270-9139
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The hepatic uptake of 45Ca was studied in rats after administration of D-galactosamine [7535-00-4] (3 mmoles/kg, i.v.). In contrast to measurements of the hepatic Ca content, 45Ca uptake served as a dynamic rather than a static indicator of **Ca homeostasis** during the transition from reversible to irreversible liver injury which occurs between 3 and 4 h after injection of the hepatotoxin. 45Ca uptake during a 1 h-labeling period increased from 25 to 100% above control between 3 and 4 h and subsequently remained at this level. The rise in 45Ca uptake and in hepatic Ca content occurred 2-3 h after the D-galactosamine-induced depletion of UTP [63-39-8], UDP-galactose [2956-16-3], UDP-glucose [133-89-1], and UDP-glucuronate [2616-64-0]. The level of UDP-glucuronate was the earliest to recover. The enhanced 45Ca uptake was assocd. with hepatic glycogen [9005-79-2] breakdown, and with an increased glutamic-pyruvic transaminase [9000-86-6] activity in plasma. Inhibition of RNA polymerase [9014-24-8] II by .alpha.-amanitin [23109-05-9] (095 mg/kg i.p.) and of dolichol-dependent protein glycosylation as well as ganglioside synthesis by tunicamycin [11089-65-9] (2 mg/kg, i.p.) were used to imitate 2 of the early actions of D-galactosamine and indicated that an interference with either process can lead to an enhanced uptake of 45Ca into the liver in vivo. Uridine [58-96-8], at a dose replenishing uracil nucleotide pools after their depletion by D-galactosamine, prevented or reversed the rise in 45Ca uptake. The antiinflammatory steroid dexamethasone [**50-02-2**], injected prior to or simultaneously with D-galactosamine also protected against the loss of **Ca homeostasis** and the development of liver injury. This action of the steroid may be related to its indirect phospholipase inhibition. The results emphasize the disturbance in **Ca homeostasis** and provide further insight into the pathogenic sequence provoked by D-galactosamine in which uridine protects at an early stage and the dexamethasone at a later stage and with less specificity for this hepatotoxin.

L70 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:417519 HCAPLUS
DOCUMENT NUMBER: 97:17519
TITLE: Submicromolar free calcium modulates dexamethasone binding to the glucocorticoid receptor
AUTHOR(S): Rousseau, Guy G.; Van Bohemen, Charles G.; Lareau, Sylvain; Degelaen, Jacques
CORPORATE SOURCE: Med. Sch., Univ. Louvain, Brussels, B-1200, Belg.
SOURCE: Biochemical and Biophysical Research Communications (1982), 106(1), 16-22
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
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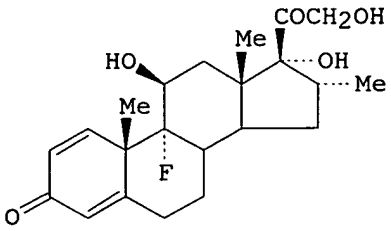

I

AB Ca decreased the affinity of dexamethasone (I) [50-02-2] for the glucocorticoid receptor in cytosol from cultured rat hepatoma cells. The rate of assocn. decreased 3-fold; the rate of dissocn. was unaffected. Ca is effective within the range of concns. at which free cytoplasmic Ca2+ exerts its 2nd messenger functions in living cells. Ca may thus act as a physiol. modulator of glucocorticoid hormone action at the receptor level.
IT **50-02-2**
RL: BIOL (Biological study)
(glucocorticoid receptor binding of, in hepatoma, **calcium regulation** of)

L70 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1973:473967 HCAPLUS
DOCUMENT NUMBER: 79:73967
TITLE: Side effects of long-time therapy with glucocorticoids on bone metabolsim
AUTHOR(S): Schmidt, Udo Juergen; Lindenhayn, Klaus; Nelius, Dieter; Muehlbach, Reiner; Haehnel, Holger; Kalbe, Irmgard
CORPORATE SOURCE: I. Med. Klin., Humboldt-Univ. Berlin, Berlin, Ger. Dem. Rep.
SOURCE: Tagungsbericht der Gesellschaft fuer Innere Medizin der Deutschen Demokratischen Republik (1972), 8, 119-22
Published in: Z. Gesamte Inn. Med. Ihre Grenzgeb. 1973, 28(17)
CODEN: TGIDAU; ISSN: 0371-6910
DOCUMENT TYPE: Journal
LANGUAGE: German
AB Dexamethasone (I) [**50-02-2**] (0.3 mg/kg/day) given to rats for 40 days produced no **osteoporotic** bone changes but increased the

porosity index and inhibited bone resorption, thus increasing bone mass. Simultaneous treatment with ethane-1-hydroxy-1,1-diphosphonate [2809-21-4] (1.0 mg P/kg/day) did not alter these effects of I treatment.

L70 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1973:427646 HCAPLUS
DOCUMENT NUMBER: 79:27646
TITLE: Action of dexamethasone and diphosphonate on bone
AUTHOR(S): Lindenhayn, K.; Schmidt, U. J.; Hirthe, D.; Wegner, G.; Kalbe, I.
CORPORATE SOURCE: Orthop. Klin., Humboldt-Univ., Berlin, Ger. Dem. Rep.
SOURCE: Deutsche Gesundheitswesen (1973), 28(5), 202-4
CODEN: DEGEA3; ISSN: 0012-0219
DOCUMENT TYPE: Journal
LANGUAGE: German
AB Dexamethasone (I) [**50-02-2**] (0.3 mg/kg/day for 40 days) increased the overall bone mass and decreased the porosity and the density of pure bone substance of femurs of rats in vivo. Its effects thus differed from **osteoporosis** produced by other corticosteroids. Simultaneous administration of 1-hydroxyethane-1,1-diphosphonate [2809-21-4] (0.3 mg/kg/day) did not alter the effects of I. The diphosphonate alone caused a significant increase in overall bone mass but no change in d. of bone substance.

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L49 1 SEA FILE=REGISTRY ABB=ON 10444-59-4/RN
L50 1 SEA FILE=REGISTRY ABB=ON 43180-35-4/RN
L51 1 SEA FILE=REGISTRY ABB=ON 1990-01-8/RN
L52 1 SEA FILE=REGISTRY ABB=ON 50-02-2/RN
L53 1 SEA FILE=REGISTRY ABB=ON 154-42-7/RN
L54 1 SEA FILE=REGISTRY ABB=ON 86-40-8/RN
L55 6 SEA FILE=REGISTRY ABB=ON L49 OR L50 OR L51 OR L52 OR L53 OR L54
L68 21265 SEA FILE=HCAPLUS ABB=ON L55
L74 93 SEA L68 AND (?PARATHYROID?(W) ?HORMONE?(W) ?RELATED?(W) ?PROTEIN? OR ?PTHRP?)
L75 58 DUP REMOV L74 (35 DUPLICATES REMOVED)
L76 39 SEA L75 AND (CALCI? OR OSTEO?)

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L76 ANSWER 1 OF 39 MEDLINE
ACCESSION NUMBER: 2002678469 MEDLINE
DOCUMENT NUMBER: 22326517 PubMed ID: 12438453
TITLE: Guanosine nucleotides inhibit different syndromes of **PTHrP** excess caused by human cancers in vivo.
COMMENT: Comment in: J Clin Invest. 2002 Nov;110(10):1399-401
AUTHOR: Gallwitz Wolfgang E; Guise Theresa A; Mundy Gregory R
CORPORATE SOURCE: OsteoScreen Ltd., San Antonio, Texas 78229, USA.. gallwitz@osteoscreen.com
CONTRACT NUMBER: P01CA40035 (NCI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (2002 Nov) 110 (10) 1559-72.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021120
Last Updated on STN: 20030202
Entered Medline: 20030131

AB There are two well-described syndromes caused by tumor production of parathyroid hormone-related peptide (**PTHrP**), namely **osteolytic** bone disease associated with breast cancer and humoral hypercalcemia of malignancy (HHM) that occurs with or without bone metastasis. Both syndromes have been shown experimentally to be inhibited by neutralizing antibodies to **PTHrP**. In a search for small-molecule inhibitors of **PTHrP** production or effects, we have identified guanine-nucleotide analogs as compounds that inhibit **PTHrP** expression by human tumor cells associated with these syndromes. We show in nude athymic murine models that these compounds reduce **PTHrP**-mediated **osteolytic** lesions associated with metastatic human breast-cancer cells as well as the degree of hypercalcemia caused by excessive **PTHrP** production by a squamous-cell carcinoma of the lung. These results suggest that the **PTHrP** gene promoter may be a suitable target for treating the skeletal effects of malignancy.

L76 ANSWER 2 OF 39 MEDLINE
ACCESSION NUMBER: 2002302726 MEDLINE
DOCUMENT NUMBER: 22028054 PubMed ID: 11897779
TITLE: Parathyroid hormone and **parathyroid hormone-related protein** exert both pro- and anti-apoptotic effects in mesenchymal cells.
AUTHOR: Chen Hen-Li; Demiralp Burak; Schneider Abraham; Koh Amy J; Silve Caroline; Wang Cun-Yu; McCauley Laurie K
CORPORATE SOURCE: Department of Periodontics, Prevention, and Geriatrics, University of Michigan, Ann Arbor, Michigan 48109, USA.
CONTRACT NUMBER: DE13788 (NIDCR)
DK53904 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 May 31) 277 (22) 19374-81.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020605
Last Updated on STN: 20030105
Entered Medline: 20020702

AB During bone formation, multipotential mesenchymal cells proliferate and differentiate into **osteoblasts**, and subsequently many die because of apoptosis. Evidence suggests that the receptor for parathyroid hormone (PTH) and **parathyroid hormone-related protein** (**PTHrP**), the PTH-1 receptor (PTH-1R), plays an important role in this process. Multipotential mesenchymal cells (C3H10T1/2) transfected with normal or mutant PTH-1Rs and MC3T3-E1 **osteoblastic** cells were used to explore the roles of PTH, **PTHrP**, and the PTH-1R in cell viability relative to **osteoblastic** differentiation. Overexpression of wild-type PTH-1R increased cell numbers and promoted **osteocalcin** gene expression

versus inactivated mutant receptors. Furthermore, the effects of PTH and **PTHrP** on apoptosis were dramatically dependent on cell status. In preconfluent C3H10T1/2 and MC3T3-E1 cells, PTH and **PTHrP** protected against dexamethasone-induced reduction in cell viability, which was dependent on cAMP activation. Conversely, PTH and **PTHrP** resulted in reduced cell viability in postconfluent cells, which was also dependent on cAMP activation. Further, the proapoptotic-like effects were associated with an inhibition of Akt phosphorylation. These data suggest that parathyroid hormones accelerate turnover of **osteoblasts** by promoting cell viability early and promoting cell departure from the differentiation program later in their developmental scheme. Both of these actions occur at least in part via the protein kinase A pathway.

L76 ANSWER 3 OF 39 MEDLINE
ACCESSION NUMBER: 2001150817 MEDLINE
DOCUMENT NUMBER: 21113008 PubMed ID: 11157145
TITLE: High concentrations of dexamethasone suppress the proliferation but not the differentiation or further maturation of human **osteoblast** precursors in vitro: relevance to glucocorticoid-induced **osteoporosis**.
AUTHOR: Walsh S; Jordan G R; Jefferiss C; Stewart K; Beresford J N
CORPORATE SOURCE: Bone Research Group, Department of Pharmacy and Pharmacology, 7 West, University of Bath, Claverton Down, Bath BA2 7AY, UK.
SOURCE: RHEUMATOLOGY, (2001 Jan) 40 (1) 74-83.
Journal code: 100883501. ISSN: 1462-0324.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20021030
Entered Medline: 20010315

AB OBJECTIVE: The use of glucocorticoids (GCs) in the treatment of RA is a frequent cause of bone loss. In vitro, however, this same class of steroids has been shown to promote the recruitment and/or maturation of primitive **osteogenic** precursors present in the colony forming unit-fibroblastic (CFU-F) fraction of human bone and marrow. In an effort to reconcile these conflicting observations, we investigated the effects of the synthetic GC dexamethasone (Dx) on parameters of growth and **osteogenic** differentiation in cultures of bone marrow stromal cells derived from a large cohort of adult human donors (n=30). METHODS: Marrow suspensions were cultured in the absence and presence of Dx at concentrations between 10 pm and 1 microm. After 28 days we determined the number and diameter of colonies formed, the total number of cells, the surface expression of receptors for selected growth factors and extracellular matrix proteins and, based on the expression of the developmental markers alkaline phosphatase (AP) and the antigen recognized by the STRO-1 monoclonal antibody, the proportion of cells undergoing **osteogenic** differentiation and their extent of maturation. RESULTS: At a physiologically equivalent concentration, Dx had no effect on the adhesion of CFU-F or on their subsequent proliferation, but did promote their **osteogenic** differentiation and further maturation. These effects were independent of changes in the expression of the receptors for fibroblast growth factors, insulin-like growth factor 1, nerve growth factor, platelet-derived growth factors and parathyroid

hormone/**parathyroid hormone-related protein**, but were associated with changes in the number of cells expressing the alpha(2) and alpha(4), but not beta(1), integrin subunits. At supraphysiological concentrations, the effects of Dx on the **osteogenic** recruitment and maturation of CFU-F and their progeny were maintained but at the expense of a decrease in cell number. CONCLUSIONS: A decrease in the proliferation of **osteogenic** precursors, but not in their differentiation or maturation, is likely to be a key factor in the genesis of GC-induced bone loss.

L76 ANSWER 4 OF 39 MEDLINE
ACCESSION NUMBER: 2001054555 MEDLINE
DOCUMENT NUMBER: 20390301 PubMed ID: 10934644
TITLE: Fibroblastic stromal cells express receptor activator of NF-kappa B ligand and support **osteoclast** differentiation.
AUTHOR: Quinn J M; Horwood N J; Elliott J; Gillespie M T; Martin T J
CORPORATE SOURCE: St. Vincent's Institute of Medical Research, Fitzroy, Victoria, Australia.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (2000 Aug) 15 (8) 1459-66.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001211

AB **Osteoclast** formation in bone is supported by **osteoblasts** expressing receptor activator of NF-kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) expression. Numerous **osteotropic** factors regulate expression levels of RANKL and the RANKL decoy receptor **osteoprotegerin** (OPG) in **osteoblasts**, thereby affecting **osteoclast** differentiation. However, not only in RANKL widely expressed in soft tissues, but **osteoclasts** have been noted in extraskeletal lesions. We found that cultured skin fibroblastic cells express RANKL, M-CSF, and OPG messenger (mRNA). Stimulation by 1 alpha,25 dihydroxyvitamin D3 [1,25(OH)2D3] plus dexamethasone (Dex) augmented RANKL and diminished OPG mRNA expression in fibroblastic cells and caused the formation of numerous **osteoclasts** in cocultures of skin fibroblastic cells with hemopoietic cells or monocytes. The **osteoclasts** thus formed expressed tartrate-resistant acid phosphatase (TRAP) and **calcitonin** (CT) receptors and formed resorption pits in cortical bone. **Osteoclast** formation also was stimulated (in the presence of Dex) by prostaglandin E2 (PGE2), interleukin-11 (IL-11), IL-1, tumor necrosis factor-alpha (TNF-alpha), and **parathyroid hormone-related protein** (**PTHrP**), factors which also stimulate **osteoclast** formation supported by **osteoblasts**. In addition, granulocyte-macrophage-CSF (GM-CSF), transforming growth factor-beta (TGF-beta), and OPG inhibited **osteoclast** formation in skin fibroblastic cell-hemopoietic cell cocultures; CT reduced only **osteoclast** nuclearity. Fibroblastic stromal cells from other tissues (lung, respiratory diaphragm, spleen, and tumor) also supported **osteoclast** formation. Thus, RANKL-positive fibroblastic cells in

extraskeletal tissues can support **osteoclastogenesis** if **osteolytic** factors and **osteoclast** precursors are present. Such mesenchymally derived cells may play a role in pathological **osteolysis** and may be involved in **osteoclast** formation in extraskeletal tissues.

L76 ANSWER 5 OF 39 MEDLINE
ACCESSION NUMBER: 1999124515 MEDLINE
DOCUMENT NUMBER: 99124515 PubMed ID: 9927325
TITLE: Human **osteoclast**-like cells are formed from peripheral blood mononuclear cells in a coculture with SaOS-2 cells transfected with the parathyroid hormone (PTH)/PTH-related protein receptor gene.
AUTHOR: Matsuzaki K; Katayama K; Takahashi Y; Nakamura I; Udagawa N; Tsurukai T; Nishinakamura R; Toyama Y; Yabe Y; Hori M; Takahashi N; Suda T
CORPORATE SOURCE: Department of Biochemistry, School of Dentistry, Showa University, Tokyo, Japan.
SOURCE: ENDOCRINOLOGY, (1999 Feb) 140 (2) 925-32.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 19990311
Entered Medline: 19990223

AB Subclones of the human **osteosarcoma** cell line SaOS-2 were established by transfecting with an expression vector containing the human PTH/PTH-related protein (**PTHrP**) receptor, and their abilities to support **osteoclast**-like multinucleated cell (OCL) formation were examined in coculture with mouse or human hemopoietic cells. Of four subclones examined, SaOS-2/4 and SaOS-4/3 bound high levels of [125I]-PTH and produced a significant amount of cAMP in response to PTH. OCLs were formed in response to PTH in the cocultures of mouse bone marrow cells with either SaOS-2/4 cells or SaOS-4/3 cells. Human OCLs were also formed in response to PTH in the coculture of SaOS-4/3 cells and human peripheral blood mononuclear cells. Adding dexamethasone together with PTH greatly enhanced PTH-induced human OCL formation. Like mouse OCLs, human OCLs formed in response to PTH were tartrate-resistant acid phosphatase positive, expressed abundant **calcitonin** receptors and vitronectin receptors, and formed resorption pits on dentine slices. Other **osteotropic** factors such as 1alpha,25-dihydroxyvitamin D3, prostaglandin E2, and interleukin 6 plus soluble interleukin 6 receptors failed to induce mouse and human OCLs in cocultures with SaOS-4/3 cells. Both mouse and human OCL formation supported by SaOS-4/3 cells were inhibited by either adding an antibody against macrophage-colony stimulating factor or adding granulocyte/macrophage-colony stimulating factor. Thus, it is likely that human and mouse OCL formation supported by SaOS-4/3 cells are similarly regulated. These results indicate that the target cells of PTH for inducing **osteoclast** formation are **osteoblast**/stromal cells but not **osteoclast** progenitor cells in the coculture. This coculture model will be useful for investigating the abnormalities ofosteoclast differentiation and function in human metabolic bone diseases.

L76 ANSWER 6 OF 39 MEDLINE

ACCESSION NUMBER: 1998210002 MEDLINE
DOCUMENT NUMBER: 98210002 PubMed ID: 9550631
TITLE: Regulation of the transcription of parathyroid-hormone/parathyroid-hormone-related peptide receptor mRNA by dexamethasone in ROS 17/2.8 **osteosarcoma** cells.
AUTHOR: Yaghoobian J; Drueke T B
CORPORATE SOURCE: INSERM Unite 90, Hopital Necker, Paris, France.
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1998 Mar) 13 (3) 580-6.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980527

AB Previous studies have shown that dexamethasone enhanced the expression of parathyroid-hormone/parathyroid-hormone-related peptide (PTH/**PTHrP**) receptor mRNA in ROS 17/2.8 **osteosarcoma** cells. The aim of this study was to determine whether the induction of PTH/**PTHrP** receptor expression in such **osteoblast**-like cells is regulated at the gene level. Dexamethasone increased the steady-state levels of PTH/**PTHrP** receptor mRNA twofold at 6 h, and nearly threefold at 24 h. The half-life of the PTH/**PTHrP** receptor mRNA, in the presence of actinomycin D, was 6 h both in untreated and in dexamethasone-treated cells. When measured by nuclear run-on assay, the rate of PTH/**PTHrP** receptor gene transcription was increased twofold at 24 h. PTH/**PTHrP** receptor mRNA expression was blocked completely after 24 h of treatment with cycloheximide. The binding of PTH/**PTHrP** to their receptor required the synthesis of new protein and was shown to be specifically dependent on the interaction of dexamethasone with the glucocorticoid receptor. These data indicate that the enhancing effect of dexamethasone on PTH/**PTHrP** receptor expression is rapid, requires de novo protein synthesis, and increases the transcription rate of the PTH/**PTHrP** receptor gene.

L76 ANSWER 7 OF 39 MEDLINE
ACCESSION NUMBER: 1998192665 MEDLINE
DOCUMENT NUMBER: 98192665 PubMed ID: 9525978
TITLE: Synovium as a source of increased amino-terminal **parathyroid hormone-related protein** expression in rheumatoid arthritis. A possible role for locally produced **parathyroid hormone-related protein** in the pathogenesis of rheumatoid arthritis.
AUTHOR: Funk J L; Cordaro L A; Wei H; Benjamin J B; Yocum D E
CORPORATE SOURCE: Department of Medicine, Arizona Arthritis Center, The University of Arizona, Tucson, Arizona 85724, USA..
jfunk@u.arizona.edu
CONTRACT NUMBER: DK-47846 (NIDDK)
HL-07479 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1998 Apr 1) 101 (7) 1362-71.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980430
Last Updated on STN: 19980430
Entered Medline: 19980423

AB Proinflammatory cytokines, including tumor necrosis factor (TNF) and interleukin 1 (IL-1), mediate the joint destruction that characterizes rheumatoid arthritis (RA). Previous studies have shown that **parathyroid hormone-related protein** (**PTHrP**) is a member of the cascade of proinflammatory cytokines induced in parenchymal organs during lethal endotoxemia. To test the hypothesis that NH2-terminal **PTHrP**, a potent bone resorbing agent, could also be a member of the synovial cascade of tissue-destructive cytokines whose expression is induced in RA, **PTHrP** expression was examined in synovium and synoviocytes obtained from patients with RA and **osteoarthritis** (OA). **PTHrP** production, as determined by measurement of immunoreactive **PTHrP**(1-86) in tissue explant supernatants, was increased 10-fold in RA versus OA synovial tissue. Synovial lining cells and fibroblast-like cells within the pannus expressed both **PTHrP** and the PTH/**PTHrP** receptor, findings that were confirmed by in vitro studies of cultured synoviocytes. TNF-alpha and IL-1beta stimulated **PTHrP** expression in synoviocytes, while dexamethasone and interferon-gamma, agents with some therapeutic efficacy in the treatment of RA, inhibited **PTHrP** release. Treatment of synoviocytes with **PTHrP** (1-34) stimulated IL-6 secretion. These results suggest that proinflammatory cytokine-stimulated production of NH2-terminal **PTHrP** by synovial tissue directly invading cartilage and bone in RA may mediate joint destruction through direct effects on cartilage or bone, or, indirectly, via the induction of mediators of bone resorption in the tumor-like synovium.

L76 ANSWER 8 OF 39 MEDLINE
ACCESSION NUMBER: 1998026747 MEDLINE
DOCUMENT NUMBER: 98026747 PubMed ID: 9362424
TITLE: **Parathyroid hormone-related protein** and bone metastases.
AUTHOR: Guise T A
CORPORATE SOURCE: Department of Medicine, University of Texas Health Science Center at San Antonio, 78284-7877, USA.
CONTRACT NUMBER: AR01899 (NIAMS)
CA69158 (NCI)
SOURCE: CANCER, (1997 Oct 15) 80 (8 Suppl) 1572-80. Ref: 67
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971120

AB **Parathyroid hormone-related protein** (PTH-rP) was purified and cloned 10 years ago as a factor responsible for

the hypercalcemia associated with malignancy. Clinical evidence supports another important role for PTH-rP in malignancy as a mediator of the bone destruction associated with **osteolytic** metastasis. Patients with PTH-rP positive breast carcinoma are more likely to develop bone metastasis. In addition, breast carcinoma metastatic to bone expresses PTH-rP in >90% of cases, compared with only 17% of metastasis to nonbone sites. These observations suggest that PTH-rP expression by breast carcinoma cells may provide a selective growth advantage in bone due to its ability to stimulate **osteoclastic** bone resorption. Furthermore, growth factors such as transforming growth factor-beta (TGF-beta), which are abundant in bone matrix, are released and activated by **osteoclastic** bone resorption and may enhance PTH-rP expression and tumor cell growth. To investigate the role of PTH-rP in the pathophysiology of breast carcinoma metastasis to bone, the human breast carcinoma cell line MDA-MB-231 was studied in a murine model of human breast carcinoma metastasis to bone. A series of experiments were performed in which 1) PTH-rP secretion was altered, 2) the effects of PTH-rP were neutralized, or 3) the responsiveness to TGF-beta was abolished in MDA-MB-231 cells. Cultured MDA-MB-231 cells secreted low amounts of PTH-rP that increased fivefold in response to TGF-beta. Tumor cells inoculated into the left cardiac ventricle of nude mice caused **osteolytic** metastasis similar to that observed in humans with breast carcinoma. When PTH-rP was overexpressed in the tumor cells, bone metastases were increased. MDA-MB-231 cells transfected with the cDNA for human preproPTH-rP secreted a tenfold greater amount of PTH-rP and caused significantly greater bone metastases when inoculated into the left cardiac ventricle of female nude mice compared with parental cells. In contrast, when the biologic effects of PTH-rP were neutralized or its production was suppressed, such metastases were decreased. Treatment of mice with a neutralizing monoclonal antibody to human PTH-rP resulted in a decrease in the development and progression of bone metastasis due to the parental MDA-MB-231 cells. Similar results were observed when mice were treated with dexamethasone, a potent glucocorticoid that suppresses production of PTH-rP by the MDA-MB-231 cells in vitro. The role of bone-derived TGF-beta in the development and progression of bone metastasis was studied by transfecting MDA-MB-231 cells with a cDNA encoding a TGF-beta type II receptor lacking a cytoplasmic domain, which acts as a dominant negative to block the cellular response to TGF-beta. Stable clones expressing this mutant receptor (MDA/TbetaRIIdeltacyt) did not increase PTH-rP secretion in response to TGF-beta stimulation compared with controls of untransfected MDA-MB-231 or those transfected with the empty vector. Mice inoculated into the left cardiac ventricle with MDA/TbetaRIIdeltacyt had fewer and smaller bone metastases as assessed radiographically and histomorphometrically compared with controls. Taken together, these data suggest that PTH-rP expression by breast carcinoma cells enhance the development and progression of breast carcinoma metastasis to bone. Furthermore, TGF-beta responsiveness of breast carcinoma cells may be important for the expression of PTH-rP in bone and the development of **osteolytic** bone metastasis in vivo. These interactions define a critical feedback loop between breast carcinoma cells and the bone microenvironment that may be responsible for the alacrity with which breast carcinoma grows in bone.

L76 ANSWER 9 OF 39 MEDLINE
ACCESSION NUMBER: 96291453 MEDLINE
DOCUMENT NUMBER: 96291453 PubMed ID: 8726387
TITLE: Glucocorticoids decrease the production of **parathyroid hormone-related**

protein in vitro but not in vivo in the Walker carcinosarcoma 256 rat model.
AUTHOR: Schilling T; Pecherstorfer M; Blind E; Kohl B; Wagner H; Ziegler R; Raue F
CORPORATE SOURCE: Department of Internal Medicine I, University of Heidelberg, Germany.
SOURCE: BONE, (1996 Apr) 18 (4) 315-9.
Journal code: 8504048. ISSN: 8756-3282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961008
Last Updated on STN: 19970203
Entered Medline: 19960924

AB In 50-90% of cases, humoral hypercalcemia of malignancy (HHM) is due to tumor secretion of **parathyroid hormone-related protein** (**PTHrP**). Glucocorticoids are sometimes used as **calcium** lowering agents and there are in vitro results showing that glucocorticoids diminish **PTHrP** production. In this study we tested whether the serum-**calcium**-lowering effect of glucocorticoids is due to decreased **PTHrP** production by the tumor. As an animal and cell culture model we used the Walker carcinosarcoma (WCS) 256, a rat mammary carcinoma cell line producing **PTHrP**. In vitro, dexamethasone caused a dose-dependent inhibition of **PTHrP** production, whereby already 1-5 nmol/L revealed a significant decrease by WCS 256 cells. In contrast to these in vitro results, in WCS 256 tumor-bearing rats, dexamethasone (4 mg/kg body weight on day 4, and 1 mg/kg body weight from day 5 until day 7 after WCS transplantation; circulating dexamethasone levels > 20 nmol/L) did not decrease **PTHrP** production, **PTHrP** secretion, serum **calcium**, or tumor weight in vivo. We conclude that, in this **PTHrP**-mediated model of humoral hypercalcemia of malignancy, glucocorticoids do not decrease **PTHrP** production and secretion in vivo and do not show a **calcium**-lowering effect.

L76 ANSWER 10 OF 39 MEDLINE
ACCESSION NUMBER: 96121531 MEDLINE
DOCUMENT NUMBER: 96121531 PubMed ID: 8557238
TITLE: 1,25 dihydroxyvitamin D and dexamethasone decrease in vivo Walker carcinoma growth, but not **parathyroid hormone related protein** secretion.
AUTHOR: Cohen-Solal M E; Bouizar Z; Denne M A; Graulet A M; Gueris J; Bracq S; Jullienne A; de Vernejoul M C
CORPORATE SOURCE: INSERM U349, Centre Viggo Petersen, Hopital Lariboisiere, Paris, France.
SOURCE: HORMONE AND METABOLIC RESEARCH, (1995 Sep) 27 (9) 403-7.
Journal code: 0177722. ISSN: 0018-5043.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960312
Last Updated on STN: 19960312
Entered Medline: 19960226

AB **Parathyroid hormone related protein** (**PTHrP**) is produced by several breast cancers. 1,25 dihydroxyvitamin D (1,25[OH]2D) and Dexamethasone (DEX) have been shown to decrease **PTHrP** mRNA expression in several cell lines. We therefore tested the in vivo effect of both steroids on **PTHrP** secretion and tumor development of the Walker carcinoma (WC). WC cells were injected subcutaneously in Fisher rats which were simultaneously treated with either vehicle, or 1,25(OH)2D (0.5 micrograms/kg/d) or DEX (2 mg/kg/d). After 7 days, tumor weight was significantly decreased in the 2 treated-groups as compared to the control group. Vehicle treated-rats developed hypercalcemia, which was also observed in rats treated with 1,25(OH)2D; by contrast, the plasma **calcium** was significantly decreased in the DEX-treated group compared to vehicle-treated rats. In a dose-effect experiment, this dose of 1,25(OH)2D induced marked hypercalcemia in rats not implanted with WC, but was required to decrease the tumor weight in implanted rats. In both 1,25(OH)2D and DEX-treated groups, plasma **PTHrP** levels were significantly decreased, but there was a similar correlation between **PTHrP** plasma level and tumor weight in the three groups. Indeed, the cytosolic **PTHrP** content/mg tumor was identical in the 3 groups. By contrast, the **PTHrP**/Actin mRNA in the tumor was significantly decreased in the 1,25(OH)2D group, comparatively to the vehicle and DEX groups. Our results show that Dexamethasone and 1,25(OH)2D decrease WC tumor development in vivo, but do not change the **PTHrP** secretion by the remaining tumor although steady state **PTHrP** mRNA content level is decreased by 1,25(OH)2D.

L76 ANSWER 11 OF 39 MEDLINE

ACCESSION NUMBER:	96042468 MEDLINE
DOCUMENT NUMBER:	96042468 PubMed ID: 7588200
TITLE:	Characterization of a novel parathyroid hormone (PTH) receptor with specificity for the carboxyl-terminal region of PTH-(1-84).
COMMENT:	Comment in: Endocrinology. 1995 Nov;136(11):4729-31
AUTHOR:	Inomata N; Akiyama M; Kubota N; Juppner H
CORPORATE SOURCE:	Department of Medicine, Massachusetts General Hospital, Boston 02114, USA.
CONTRACT NUMBER:	DK-11794 (NIDDK)
SOURCE:	ENDOCRINOLOGY, (1995 Nov) 136 (11) 4732-40. Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:	199511
ENTRY DATE:	Entered STN: 19960124 Last Updated on STN: 19960124 Entered Medline: 19951127

AB Carboxyl-terminal fragments of PTH (C-PTH) appear to have biological properties different from those mediated by the amino-terminal portions of PTH and PTH-related peptide (**PTHrP**). To characterize a C-PTH receptor that may be involved in mediating these functions, we performed RRAs and affinity cross-linking studies with several clonal cell lines. Radiolabeled recombinant [Leu8,18,Tyr34]human PTH-(1-84)[mutPTH-(1-84) and [Tyr34] human PTH-(19-84)[mutPTH-(19-84) showed little or no specific binding to stably expressed recombinant PTH/**PTHrP** receptors. However, high affinity binding was observed using **osteoblast** -like and rat parathyroid (PT-r3) cells. The apparent Kd values were 20-30

nM for PTH-(1-84), mutPTH-(1-84), and mutPTH-(19-84), respectively; 400-800 nM for PTH-(39-84); and more than 5000 nM for PTH-(53-84). [Nle8,18,Tyr34]bovine PTH-(1-34)amide [PTH-(1-34)], PTH-(44-68), **PTHrP**-(37-74), and **PTHrP**-(109-141) showed no displacement of either radioligand. C-PTH receptor number was increased up to 2-fold by pretreating ROS 17/2.8 cells with increasing doses of PTH-(1-34), PTH-(1-84), or 8-bromo-cAMP, whereas no change was observed in response to dexamethasone or PTH-(39-84). Cross-linking studies using radiolabeled mutPTH-(1-84) or mutPTH-(19-84) revealed specific labeling of two proteins in ROS 17/2.8 cells that were approximately 40 and 90 kilodaltons in size (including the radioligand of approximately 10 kilodaltons). The intensity of affinity labeling of both proteins was dose dependently inhibited by increasing concentrations of unlabeled PTH-(1-84) and several carboxyl-terminal PTH-(1-84) fragments, but not by PTH-(1-34). Similar studies with PT-r3 cells revealed only a single protein band of about 90 kilodaltons. These data indicate that the carboxyl-terminal portion of PTH-(1-84) binds specifically to a unique receptor/binding protein distinct from the previously isolated PTH/**PTHrP** receptor.

L76 ANSWER 12 OF 39 MEDLINE
ACCESSION NUMBER: 96038739 MEDLINE
DOCUMENT NUMBER: 96038739 PubMed ID: 7581942
TITLE: Amniotic fluid and plasma levels of **parathyroid hormone-related protein** and hormonal modulation of its secretion by amniotic fluid cells.
COMMENT: Comment in: Eur J Endocrinol. 1995 Sep;133(3):272-4
AUTHOR: Dvir R; Golander A; Jaccard N; Yedwab G; Otremski I; Spirer Z; Weisman Y
CORPORATE SOURCE: Bone Disease Unit, Tel-Aviv Sourasky Medical Center, Israel.
SOURCE: EUROPEAN JOURNAL OF ENDOCRINOLOGY, (1995 Sep) 133 (3) 277-82.
Journal code: 9423848. ISSN: 0804-4643.
PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 20021217
Entered Medline: 19951130

AB Parathyroid hormone-related (**PTHrP**), the major mediator of humoral hypercalcemia of malignancy, may also regulate placental **calcium** flux, uterine contraction and fetal tissue development. In the present study, we demonstrated that the mean immunoreactive **PTHrP** concentrations in amniotic fluid at mid-gestation (21.2 +/- 3.7 pmol/l) and at term (19.0 +/- 2.7 pmol/l) were 13-16-fold higher than levels measured in either fetal (1.6 +/- 0.1 pmol/l) or maternal plasma (1.4 +/- 0.3 pmol/l) at term and equal to levels found in plasma of patients with humoral hypercalcemia of malignancy. In vitro studies pointed to three possible sources of **PTHrP** in amniotic fluid: cultured amniotic fluid cells, cells derived from the amniotic membrane overlying the placenta and placental villous core mesenchymal cells. Treatment of cultured amniotic fluid cells with human prolactin, human placental lactogen (hPL) or human growth hormone (100 micrograms/l) increased **PTHrP** secretion after 24 h by 43%, 109% and 90%,

respectively. Insulin-like growth factors I and II (100 micrograms/l), insulin (100 micrograms/l) and epidermal growth factor (EGF) (10 micrograms/l) increased **PTHrP** secretion by 53%, 46%, 68% and 118%, respectively. The stimulation of **PTHrP** secretion by EGF or by hPL was both time- and dose-dependent. In contrast, **calcitriol** and dexamethasone (10 nmol/l) decreased **PTHrP** secretion by 32% and 75%, respectively. Estradiol, progesterone, dihydrotestosterone and human chorionic gonadotropin had no effect on **PTHrP** secretion. These findings support the notion that **PTHrP** may play a physiological role in the uteroplacental unit and demonstrate that human amniotic fluid cells could be a useful model for studying the regulation of **PTHrP** production and secretion by hormones and growth factors.

L76 ANSWER 13 OF 39 MEDLINE
ACCESSION NUMBER: 95131119 MEDLINE
DOCUMENT NUMBER: 95131119 PubMed ID: 7829996
TITLE: Regulation of **parathyroid hormone-related protein** production in a human lung squamous cell carcinoma line.
AUTHOR: Rizzoli R; Feyen J H; Grau G; Wohlwend A; Sappino A P; Bonjour J P
CORPORATE SOURCE: Department of Medicine, University Hospital, Geneva, Switzerland.
SOURCE: JOURNAL OF ENDOCRINOLOGY, (1994 Nov) 143 (2) 333-41. Journal code: 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950307
Last Updated on STN: 19970203
Entered Medline: 19950222

AB The synthesis and release of **parathyroid hormone-related protein** (**PTHrP**) could be influenced in a paracrine or autocrine manner by substances present around or inside tumours, such as bone or stromal cell-derived cytokines, factors produced by the tumour itself or by peritumoural inflammatory cells. We investigated the effects of various cytokines known to be synthesized by **osteoblasts**, stromal cells, leucocytes or cancer cells, on **PTHrP** production by the human lung squamous cell carcinoma line BEN. The influence of tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) was studied, and compared with those of insulin-like growth factors-I and -II (IGF-I, IGF-II), or macrophage- or granulocyte-macrophage colony-stimulating factors (M-CSF, GM-CSF). TNF-alpha caused a 1.9 +/- 0.1-fold increase in immunoreactive **PTHrP** production, which was maximal by 24 h of incubation. IL-6 caused a 2.3 +/- 0.2-fold increase, which was maximal by 16 h. These effects, which were time- and concentration-dependent, were blocked by monoclonal antibodies raised against the corresponding cytokine. An increase of **PTHrP** mRNA was found in IL-6-treated cells. IGF-I and IGF-II increased **PTHrP** production by 2.0 +/- 0.3- and 2.3 +/- 0.1-fold respectively. Neither M-CSF nor GM-CSF altered **PTHrP** production up to 64 h of incubation. **PTHrP** production was not affected by varying extracellular **calcium** concentrations, but was decreased by incubation with 100 nmol/l dexamethasone.(ABSTRACT TRUNCATED AT 250 WORDS)

L76 ANSWER 14 OF 39 MEDLINE
ACCESSION NUMBER: 93215536 MEDLINE
DOCUMENT NUMBER: 93215536 PubMed ID: 8462465
TITLE: Regulation of parathyroid hormone-related peptide production in vitro by the rat hypercalcemic Leydig cell tumor H-500.
AUTHOR: Liu B; Goltzman D; Rabbani S A
CORPORATE SOURCE: Department of Medicine, McGill University, Montreal, Quebec, Canada.
SOURCE: ENDOCRINOLOGY, (1993 Apr) 132 (4) 1658-64.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 20000303
Entered Medline: 19930430

AB The transplantable rat Leydig cell tumor H-500 is known to cause hypercalcemia in vivo by the release of abundant PTH-related peptide (**PTHRP**) and to closely reproduce the human syndrome of malignancy-associated hypercalcemia. In the rat only a single messenger RNA species of 1.4 kilobases is expressed which encodes a peptide of 141 amino acid as the sole molecular form. We have examined in cultured rat Leydig tumor cells H-500, the capacity of multiple factors to regulate **PTHRP** messenger RNA expression and secretion. Both fetal bovine serum and epidermal growth factor stimulated **PTHRP** gene expression and secretion into conditioned culture medium. Dexamethasone and 1,25-dihydroxyvitamin D3 produced inhibition of **PTHRP** gene expression and secretion. Furthermore, in these testicular cells, after 12 h or more of incubation, testosterone produced a dose-dependent (10(-9)-10(-7) M) inhibition of **PTHRP** production. No significant difference in this inhibitory response was seen between testosterone and its 5 alpha-reduced metabolite dihydrotestosterone whereas 17 beta-estradiol, progesterone, LH, FSH, and PRL were ineffective. An androgen receptor antagonist Win 49596 blocked the androgen-mediated inhibition of **PTHRP** gene expression and secretion, but not that due to dexamethasone. Epidermal growth factor caused an increase, whereas androgen caused a decrease in **PTHRP** gene transcription. These studies demonstrated that growth factors, dexamethasone, and 1,25-dihydroxyvitamin D3 are broadly active regulatory agents of **PTHRP** production which cross species and tissue barriers. Testosterone may be a more selective modulator which can regulate **PTHRP** in tissues such as Leydig cell neoplasms which express the androgen receptor.

L76 ANSWER 15 OF 39 MEDLINE
ACCESSION NUMBER: 92274370 MEDLINE
DOCUMENT NUMBER: 92274370 PubMed ID: 1591723
TITLE: Parathyroid hormone-like peptide shares features with members of the early response gene family: rapid induction by serum, growth factors, and cycloheximide.
AUTHOR: Allinson E T; Drucker D J
CORPORATE SOURCE: Department of Clinical Biochemistry, University of Toronto, Ontario, Canada.
SOURCE: CANCER RESEARCH, (1992 Jun 1) 52 (11) 3103-9.

Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920710
Last Updated on STN: 20000303
Entered Medline: 19920630

AB The parathyroid hormone-like peptide (PLP) gene is widely expressed in normal and neoplastic tissues. Previous studies have demonstrated that PLP gene expression is regulated by serum and cycloheximide, features common to the regulation of a number of different early response genes. We now report that PLP mRNA transcripts are induced within 5 min of exposure of rat keratinocytes to serum, return to control values at 20 min, and then increase and remain elevated for at least 4 h, following which they return to baseline levels. The PLP mRNA t1/2 was approximately 90 min in both serum-deprived and serum-stimulated cells. The serum induction was blocked by actinomycin D. Cycloheximide alone induced PLP gene expression; however, PLP mRNA transcripts were not superinduced in the presence of both serum and cycloheximide. Dexamethasone and 1,25-dihydroxyvitamin D3 inhibited the basal levels of PLP mRNA transcripts but did not eliminate the serum induction of PLP gene expression. Epidermal growth factor or transforming growth factor-beta alone induced PLP mRNA transcripts, but no induction was observed following exposure of cells to epidermal growth factor and transforming growth factor-beta together. Treatment with 12-O-tetradecanoylphorbol-13-acetate for 90 min did not induce PLP mRNA transcripts, but 12-O-tetradecanoylphorbol-13-acetate blocked the rapid serum induction of PLP gene expression. These features of PLP gene expression suggest that PLP is a member of the growth factor-regulated early response gene family. The rapid serum stimulation of PLP gene expression raises the possibility that PLP may contribute in an autocrine fashion to the early cellular response to growth factor stimulation.

L76 ANSWER 16 OF 39 MEDLINE
ACCESSION NUMBER: 91257767 MEDLINE
DOCUMENT NUMBER: 91257767 PubMed ID: 1646150
TITLE: **Osteolytic** activity of Walker carcinosarcoma 256 is due to **parathyroid hormone-related protein (PTHrP)**.
AUTHOR: Scharla S H; Minne H W; Lempert U G; Krieg P; Rappel S; Maurer E; Grohe U; Ziegler R
CORPORATE SOURCE: Abteilung Innere Medizin I, Endokrinologie und Stoffwechsel, Klinikum der Universitat Heidelberg, Germany.
SOURCE: HORMONE AND METABOLIC RESEARCH, (1991 Feb) 23 (2) 66-9.
Journal code: 0177722. ISSN: 0018-5043.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910802
Last Updated on STN: 19980206
Entered Medline: 19910716

AB The hypercalcemic Walker carcinosarcoma 256 of the rat is an animal model for humoral hypercalcemia of malignancy. Previous in vivo studies suggested the production of a **parathyroid hormone-related protein (PTHrP)** by the Walker tumor.

Therefore, we have measured immunoreactive **PTHrP** in serum-free conditioned medium from cells derived from this tumor using an antibody raised against human **PTHrP**(1-34). Walker tumor cell conditioned medium (WCM) displaced 125I-**hPTHrP**(1-34) from the antibody in a dose dependent manner, whereas control medium contained no immunoreactive **PTHrP**. In contrast, we detected no secretion of immunoreactive rat parathyroid hormone (rat PTH) by the Walker tumor cells using a midregional radioimmunoassay for rat PTH. WCM stimulated adenylate cyclase in **osteoblast** like cells, the dose-response curve paralleling that of **hPTHrP**(1-34). This effect could be inhibited by the PTH antagonist (8Nle, 18Nle, 34Tyr)bPTH(3-34) and by the addition of anti-**hPTHrP**(1-34) antibody. Bone resorbing activity of WCM in organ culture (calvaria of fetal rats) was not inhibited by indomethacin and glucocorticoids, suggesting a prostaglandin independent mechanism of **osteoclast** activation in this model.

L76 ANSWER 17 OF 39 MEDLINE
ACCESSION NUMBER: 90298905 MEDLINE
DOCUMENT NUMBER: 90298905 PubMed ID: 2163326
TITLE: Treatment of bone-derived ROS 17/2.8 cells with dexamethasone and pertussis toxin enables detection of partial agonist activity for parathyroid hormone antagonists.
AUTHOR: McKee R L; Caulfield M P; Rosenblatt M
CORPORATE SOURCE: Parathyroid Hormone Laboratory, Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486.
SOURCE: ENDOCRINOLOGY, (1990 Jul) 127 (1) 76-82.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900907
Last Updated on STN: 20021218
Entered Medline: 19900808

AB In the design and biological evaluation of PTH antagonists, certain analogs, although antagonists in vitro, possess partial agonist properties in vivo that preclude their utility as antagonists. In an effort to identify weak agonism of PTH analogs, an attempt was made to enhance the responsiveness of the widely employed rat **osteosarcoma** (ROS 17/2.8) cell adenylate cyclase assay. Because responsiveness to PTH in these cells is enhanced upon treatment with dexamethasone (dex) or pertussis toxin (PT), we have evaluated their use to aid in detection of partial agonism for PTH and PTH-related protein (**PTHrP**) antagonist analogs. Treatment of cells with dex alone (30 nM for 3 days) or with PT alone (40 ng/ml for 1 day) increased basal adenylate cyclase activity by 27%. However, combination of the dex and PT treatments increased basal cAMP production 70%. The in vivo partial agonist [Nle8,18,Tyr34]bPTH(3-34)NH2 increased cAMP production 3-fold over basal levels in untreated cells, nearly 5-fold in PT-treated cells, 8-fold in cells treated with dex, and 10-fold in cells treated with dex plus PT. Similar results were obtained with **PTHrP**(7-34)NH2: the 6-fold stimulation observed in control cells was converted to 14-fold in cells treated with dex plus PT. Agonist activity undetectable in the conventional assay was observed in the dex plus PT system: [Tyr34]- and [D-Trp12,Tyr34]bPTH(7-34)NH2, which exhibit no agonist activity under control conditions, stimulated cAMP production 2.6- and 2.1-fold,

respectively, under dex plus PT treatment. In contrast, the antagonist analogs [Asn10,Leu11]- and [Leu11,D-Trp12]**PTHrP**(7-34)NH2, hybrid peptides of PTH and **PTHrP**, had no agonist activity under any conditions. Because of increased responsiveness, this assay should occupy an important step in the pathway for evaluation of PTH antagonists and permit identification of weak partial agonist activity before extensive in vivo testing.

L76 ANSWER 18 OF 39 MEDLINE
ACCESSION NUMBER: 89380153 MEDLINE
DOCUMENT NUMBER: 89380153 PubMed ID: 2777759
TITLE: Transcriptional regulation of the parathyroid hormone-related peptide gene by glucocorticoids and vitamin D in a human C-cell line.
AUTHOR: Ikeda K; Lu C; Weir E C; Mangin M; Broadus A E
CORPORATE SOURCE: Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06510.
CONTRACT NUMBER: AR-30102 (NIAMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1989 Sep 25) 264 (27) 15743-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19891025

AB A parathyroid hormone-related peptide (**PTHRP**) has been identified in human tumors associated with the syndrome of humoral hypercalcemia of malignancy. The **PTHRP** and parathyroid hormone (PTH) genes appear to have arisen by duplication and to represent members of a gene family. **PTHRP** mRNAs have been demonstrated in a number of normal tissues, but little is known concerning the regulation of **PTHRP** gene expression in any site. We studied **PTHRP** gene expression in TT cells, a human C-cell line which also produces **calcitonin** and **calcitonin** gene-related peptide. We found that both the synthetic glucocorticoid, dexamethasone, and the active vitamin D metabolite, 1,25-dihydroxyvitamin D3, decreased steady-state **PTHRP** mRNA levels in TT cells in a time- and dose-dependent fashion. The dexamethasone effect was completely blocked by the glucocorticoid antagonist RU-486. 24,25-dihydroxyvitamin D3 was found to be inactive. Neither dexamethasone nor 1,25-dihydroxyvitamin D3 appeared to influence **PTHRP** mRNA stability in TT cells, and both agents were shown by nuclear transcription run-off assay to decrease **PTHRP** gene transcription. These findings indicate that the **PTHRP** gene is under the transcriptional control of glucocorticoids and vitamin D in a cell line with prototypical neuroendocrine features.

L76 ANSWER 19 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:208216 BIOSIS
DOCUMENT NUMBER: PREV200200208216
TITLE: Exposure of KS483 cells to estrogen enhances **osteogenesis** and inhibits adipogenesis.
AUTHOR(S): Dang, Z. C.; van Bezooijen, R. L.; Karperien, M.; Papapoulos, S. E.; Lowik, C. W. G. M. (1)
CORPORATE SOURCE: (1) Department of Endocrinology and Metabolic Diseases,

Leiden University Medical Center, Albinusdreef 2, C4-R, 2300 RC, Leiden Netherlands
SOURCE: Journal of Bone and Mineral Research, (March, 2002) Vol. 17, No. 3, pp. 394-405. print.
ISSN: 0884-0431.
DOCUMENT TYPE: Article
LANGUAGE: English
AB **Osteoblasts** and adipocytes arise from a common progenitor cell in bone marrow. Whether estrogen directly regulates the progenitor cells differentiating into **osteoblasts** or adipocytes remains unknown. Using a mouse clonal cell line KS483 cultured in charcoal-stripped fetal bovine serum (FBS), we showed that 17beta-estradiol (E2) stimulates the differentiation of progenitor cells into **osteoblasts** and concurrently inhibits adipocyte formation in an estrogen receptor (ER)-dependent way. E2 increased alkaline phosphate (ALP) activity and nodule formation and stimulated messenger RNA (mRNA) expression of core-binding factor alpha-1 (Cbfa1), parathyroid hormone/**parathyroid hormone-related protein** receptors (PTH/**PTHrP**-Rs), and **osteocalcin**. In contrast, E2 decreased adipocyte numbers and down-regulated mRNA expression of peroxisome proliferator-activated receptor-gamma (PPARgamma)2, adipocyte protein 2 (aP2), and lipoprotein lipase (LPL). Furthermore, the reciprocal control of **osteoblast** and adipocyte differentiation by E2 was observed also in the presence of the adipogenic mixture of isobutylmethylxanthine, dexamethasone, and insulin. Immunohistochemical staining showed that ERalpha and ERbeta were present in **osteoblasts** and adipocytes. A new mouse splice variant ERbeta2 was identified, which differed in two amino acid residues from the rat isoform. E2 down-regulated mRNA expression of ERalpha, ERbeta1, and ERbeta2. The effects of E2 are not restricted to the KS483 cell line because similar results were obtained in mouse bone marrow cell cultures. Our results indicate that estrogen, in addition to stimulation of **osteogenesis**, inhibits adipogenesis, which might explain the clinical observations that estrogen-deficiency leads to an increase in adipocytes.

L76 ANSWER 20 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:289225 BIOSIS
DOCUMENT NUMBER: PREV199900289225
TITLE: Effect of EGF, estradiol, 1,25 dihydroxycholicalciferol, and dexamethasone on PTH/**PTHrP** receptor affinity in MCF7 breast cancer and SaOS-2 **osteosarcoma** cells.
AUTHOR(S): Alokail, M. S. (1); Peddie, M. J. (1)
CORPORATE SOURCE: (1) Division of Cell Sciences, School of Biological Sciences, University of Southampton, Bassett Crescent East, Biomedical Sciences Building, Southampton, S016 7PX UK
SOURCE: Journal of Endocrinology, (March, 1999) Vol. 160, No. SUPPL., pp. P184.
Meeting Info.: 18th Joint Meeting of the British Endocrine Societies Bournemouth, England, UK April 12-15, 1999 British Endocrine Societies
. ISSN: 0022-0795.
DOCUMENT TYPE: Conference
LANGUAGE: English

L76 ANSWER 21 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:289224 BIOSIS

DOCUMENT NUMBER: PREV199900289224
TITLE: Regulation of PTH/**PTHrP** receptor expression in MCF7 breast cancer and SaOS-2 **osteosarcoma** cells by dexamethasone, 1,25 DHCC, EGF, E2, and **PTHrP** -1-34.
AUTHOR(S): Alokail, M. S. (1); Peddie, M. J. (1)
CORPORATE SOURCE: (1) Division of Cell Sciences, School of Biological Sciences, University of Southampton, Bassett Crescent East, Biomedical Sciences Building, Southampton, SO16 7PX UK
SOURCE: Journal of Endocrinology, (March, 1999) Vol. 160, No. SUPPL., pp. P183.
Meeting Info.: 18th Joint Meeting of the British Endocrine Societies Bournemouth, England, UK April 12-15, 1999 British Endocrine Societies
. ISSN: 0022-0795.
DOCUMENT TYPE: Conference
LANGUAGE: English

L76 ANSWER 22 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:269248 BIOSIS
DOCUMENT NUMBER: PREV199799560966
TITLE: Dexamethasone stimulates **osteoclast**-like cell formation by directly acting on hemopoietic blast cells and enhances **osteoclast**-like cell formation stimulated by parathyroid hormone and prostaglandin E-2.
AUTHOR(S): Kaji, Hiroshi; Sugimoto, Toshitsugu (1); Kanatani, Masanori; Nishiyama, Katsuhito; Chihara, Kazuo
CORPORATE SOURCE: (1) Third Div., Dep. Med., Kobe Univ. Sch. Med., 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650 Japan
SOURCE: Journal of Bone and Mineral Research, (1997) Vol. 12, No. 5, pp. 734-741.
ISSN: 0884-0431.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Although an excess of glucocorticoid induces secondary **osteoporosis**, the mechanism still remains unclear, particularly in regard to glucocorticoid-stimulated bone resorption. We examined the effects of dexamethasone (Dex) on **osteoclast**-like cell formation and bone-resorbing activity by employing mouse bone and spleen cell cultures and further investigated whether Dex would modulate **osteoclast**-like cell formation stimulated by several bone-resorbing factors. Dex stimulated **osteoclast**-like cell formation in stromal cell-containing mouse bone cell cultures in a concentration-dependent manner. Also, Dex significantly stimulated **osteoclast**-like cell formation from hemopoietic blast cells in spleen cell cultures derived from 5-fluorouracil-pretreated mice. In contrast, Dex (10-8 M) did not affect the bone-resorbing activity of mature **osteoclasts**. Pretreatment with 10-8 M Dex significantly enhanced **osteoclast**-like cell formation in unfractionated mouse bone cell cultures stimulated by 10-8 M human (h) parathyroid hormone (PTH) (1-34), 10-8 M hPTH-related protein (1-34) and 10-6 M prostaglandin E-2, but not by 10-8 M 1,25-dihydroxyvitamin D-3 (1,25(OH)-2D-3). Moreover, pretreatment with 10-8 M Dex significantly enhanced **osteoclast**-like cell formation stimulated by both forskolin and dbcAMP. In contrast, pretreatment with 10-8 M Dex significantly inhibited **osteoclast**-like cell formation in mouse spleen cell cultures stimulated by both 10-8 M hPTH(1-34) and 10-8 M 1,25(OH)-2D-3. These findings suggest that Dex stimulates **osteoclast**-like cell

formation, at least in part by directly acting on hemopoietic blast cells. They further suggest that Dex enhances **osteoclast**-like cell formation stimulated by PTH and prostaglandin E-2 through an indirect pathway via cells other than hemopoietic blast cells.

L76 ANSWER 23 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:218388 BIOSIS
DOCUMENT NUMBER: PREV199698774517
TITLE: Cell-specific and regulator-induced promoter usage and messenger ribonucleic acid splicing for **parathyroid hormone-related protein**.
AUTHOR(S): Southby, Justine; Murphy, Leonie M.; Martin, T. John; Gillespie, Matthew T. (1)
CORPORATE SOURCE: (1) St. Vincent's Inst. Med. Res., 41 Victoria Parade, Fitzroy 3065, VIC Australia
SOURCE: Endocrinology, (1996) Vol. 137, No. 4, pp. 1349-1357. ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
AB PTH-related protein (**PTHrP**) is the principle mediator of the syndrome of humoral hypercalcemia of malignancy and has potential paracrine actions on smooth muscle, epithelial cell growth, and placental **calcium** transport. The human **PTHrP** gene is complex: a combination of three promoters, one 5' alternative splicing event and alternative 3' splicing, which produces three **PTHrP** isoforms (139, 141, or 173 amino acids), results in multiple **PTHrP** messenger RNA (mRNA) species. We employed the RT-PCR technique to identify promoter usage and splicing patterns in a range of human cell lines. Cell line-specific utilization of the promoters and the 3' alternative splicing pathways was detected among bone, breast, kidney, and lung cell lines, although each cell line could potentially produce the three **PTHrP** isoforms. We also determined whether some of the known regulators of **PTHrP** differentially modulate promoter usage or splicing patterns. Dexamethasone decreased the abundance of each of the alternative mRNA species. In contrast, epidermal growth factor and transforming growth factor-beta treatment increased the abundance of each **PTHrP** mRNA species, with particularly marked effects on promoter 1- and promoter 2-initiated transcripts, especially those containing exon VII or VIII. Epidermal growth factor treatment was found to alter **PTHrP** splicing patterns in a manner consistent with increased transcription from promoters 1 and 2 and stabilization of exon VII- and IX-containing transcripts.

L76 ANSWER 24 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002423128 EMBASE
TITLE: Preterm delivery.
AUTHOR: Slattery M.M.; Morrison J.J.
CORPORATE SOURCE: Dr. J.J. Morrison, Department of Obstetrics, Natl. University of Ireland Galway, Clinical Science Institute, Galway, Ireland. john.morrison@nuigalway.ie
SOURCE: Lancet, (9 Nov 2002) 360/9344 (1489-1497). Refs: 140
ISSN: 0140-6736 CODEN: LANCAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
010 Obstetrics and Gynecology
017 Public Health, Social Medicine and Epidemiology

037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Preterm delivery and its short-term and long-term sequelae constitute a serious problem in terms of mortality, disability, and cost to society. The incidence of preterm delivery, which has increased in recent years, is associated with various epidemiological and clinical risk factors. Results of randomised controlled trials suggest that attempts to reduce these risk factors by use of drugs are limited by side-effects and poor efficacy. An improved understanding of the physiological pathways that regulate uterine contraction and relaxation in animals and people has, however, helped to define the complex processes that underlie parturition (term and preterm), and has led to new scientific approaches for myometrial modulation. The continuing elucidation of the mechanisms that regulate preterm labour, combined with rigorous clinical assessment, offer hope for future solutions.

L76 ANSWER 25 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002305726 EMBASE
TITLE: Cyclic adenosine monophosphate/protein kinase A mediates parathyroid hormone/**parathyroid hormone -related protein** receptor regulation of **osteoclastogenesis** and expression of RANKL and **osteoprotegerin** mRNAs by marrow stromal cells.
AUTHOR: Kondo H.; Guo J.; Bringhurst F.R.
CORPORATE SOURCE: Dr. F.R. Bringhurst, Endocrine Unit, Massachusetts General Hospital, Wellman 501, 50 Blossom Street, Boston, MA 02114, United States
SOURCE: Journal of Bone and Mineral Research, (2002) 17/9 (1667-1679).
Refs: 79
ISSN: 0884-0431 CODEN: JBMREJ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Parathyroid hormone (PTH) is a major regulator of **osteoclast** formation and activation, effects that are associated with reciprocal up- and down-regulation of RANKL and **osteoprotegerin** (OPG), respectively. The roles of specific downstream signals generated by the activated PTH/PTH-related protein (**PTHrP**) receptor (PTH1R), such as cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) and phospholipase C/protein kinase C (PLC/PKC), in controlling RANKL and OPG expression and **osteoclastogenesis** remain uncertain. In MS1 conditionally transformed clonal murine marrow stromal cells, which support PTH-induced **osteoclast** formation from cocultured normal spleen cells, PTH(1-34) increased RANKL and macro-phage colony-stimulating factor (M-CSF) mRNA expression and decreased that of OPG when present continuously for 7-20 days at 37.degree.C in the presence of dexamethasone (Dex). In cells precultured for 7 days and then treated with PTH(1-34), similar reciprocal regulation of RANKL and OPG occurred, maximally at 6-24 h, that was of greater amplitude than the changes induced by chronic (7-10 days) PTH exposure. These acute effects of PTH(1-34) were mimicked by PKA stimulators (8-bromoadenosine [8Br]-cAMP or forskolin [FSK]), blocked by

the PKA inhibitor Rp-cAMPs but unaffected by the PKC inhibitor GF109203X. Amino-truncated PTH(1-34) analogs PTH(5-34) and PTH(7-34) neither increased cAMP production in MS1 cells nor regulated RANKL or OPG mRNA. Reciprocal RANKL/OPG mRNA regulation was induced in MS1 cells by PTH(3-34) but only at high concentrations that also increased cAMP. The highly PKA-selective PTH analog [Gly(1),Arg(19)]human PTH(1-28) exerted effects similar to PTH(1-34) on RANKL and OPG mRNAs and on **osteoclast** formation, both in MS1/spleen cell cocultures and in normal murine bone marrow cultures. The direct PKC stimulator 12-O-tetradecanoylphorbol-13-acetate (PMA) did not induce RANKL mRNA in MS1 cells, but it did up-regulate OPG mRNA and also antagonized **osteoclast** formation induced by PTH(1-34) in both MS1/spleen cocultures and normal bone marrow cultures. Thus, cAMP/PKA signaling via the PTH1R is the primary mechanism for controlling RANKL-dependent **osteoclastogenesis**, although direct PKC activation may negatively regulate this effect of PTH by inducing expression of OPG.

L76 ANSWER 26 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002184540 EMBASE
TITLE: Ascites sarcoma 180 secretes a soluble factor (s) which inhibits mineralized nodule formation In Vitro.
AUTHOR: Suzuki K.; Yamada S.
CORPORATE SOURCE: K. Suzuki, Department of Pharmacology, School of Dentistry, Showa University, Showa, Japan
SOURCE: Oral Therapeutics and Pharmacology, (2001) 20/3 (186-195). Refs: 30
ISSN: 0288-1012 CODEN: SYRYEJ
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English; Japanese
AB Ascites sarcoma 180 (S180A) is a transplantable tumor that induces hypercalcemia in tumor-bearing mice without producing **parathyroid hormone-related protein** (**PTHrP**) and stimulates bone resorption in cultured neonatal mouse calvaria. To investigate the effects of S180A on bone formation, bone marrow cells were cultured in the presence of ascorbic acid, dexamethasone and .beta.-glycerophosphate and then cell proliferation and mineralized nodule formation were evaluated. Serum-free conditioned media of ascites cell cultures greatly stimulated the (3)H-thymidine uptake (5.5-fold on day 10) throughout the experimental period up to 14 days. On the other hand, they limited the rise in alkaline phosphatase activity significantly compared to control (44.1% and 70.8% of control on day 10 and 14, respectively). After 14 days of culture, many mineralized nodules were observed in control and recombinant human TGF groups, whereas nodule formation was completely abolished by the addition of S180A CM. Thus the results of the present study indicate that tumor-produced factors cause hypercalcemia by inhibiting bone formation, which cooperates with the stimulation of bone resorption in S180A-bearing mice.

L76 ANSWER 27 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002100881 EMBASE
TITLE: PTH receptors and apoptosis in **osteocytes**.
AUTHOR: Bringhurst F.R.
CORPORATE SOURCE: Dr. F.R. Bringhurst, Endocrine Unit, Massachusetts General

Hospital, Fruit Street, Boston, MA 02114, United States.
rbringhurst@partners.org
SOURCE: Journal of Musculoskeletal Neuronal Interactions, (2002) 2/3 (245-251).
Refs: 73
ISSN: 1108-7161 CODEN: JMNIB3
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Osteocytes** comprise a heterogenous population of terminally differentiated **osteoblasts** that direct bone remodeling in response to applied mechanical loading of bone. Increased **osteocyte** density accompanies the anabolic effect of PTH in vivo, whereas accelerated **osteocyte** death may be precipitated by estrogen deficiency or excess glucocorticoid exposure (conditions benefitted by intermittent PTH therapy) and by renal failure (where circulating intact PTH and, especially, PTH carboxyl-fragments are elevated). **Osteocytes** express type-1 PTH/**PTHrP** receptors (PTH1Rs), which are fully activated by amino-terminal PTH fragments and couple to multiple signal transducers, including adenylyl cyclase and phospholipase C. Activation of PTH1Rs in **osteocytes** promotes gap junction-mediated intercellular coupling, increases expression of MMP-9, potentiates **calcium** influx via stretch-activated cation channels, amplifies the **osteogenic** response to mechanical loading in vivo, and regulates apoptosis. Control of **osteocyte** apoptosis by PTH1Rs is complex, in that intermittent PTH(1-34) administration reduces the fraction of vertebral apoptotic **osteocytes** at 1 month in adult mice but increases femoral metaphyseal **osteocyte** apoptosis at 1-2 weeks in young rats. In MLO-Y4 cells, PTH(1-34) prevents apoptosis otherwise induced within 6 hr by dexamethasone. In older studies, large doses of intact PTH(1-84) caused rapid "degenerative" morphologic changes in **osteocytes**, similar to those described in renal **osteodystrophy**. We isolated clonal conditionally immortalized **osteocytic** (OC) cell lines from mice homozygous for targeted ablation of the PTH1R gene. OC cells express abundant (2-3 x 10(6) per cell) receptors specific for the carboxyl(C)-terminus of intact PTH(1-84) ("CPTHRs") but, as expected, do not express PTH1Rs or respond to PTH(1-34). CPTHRs are expressed at much lower levels by other skeletally-derived cell lines. Several highly conserved ligand determinants of CPTHR binding have been identified, including PTH(24-27), PTH(53-54) and the sequence PTH(55-84), loss of which reduces binding affinity by over 100-fold. Human PTH(53-84), like PTH(1-84), PTH(24-84), and PTH(39-84), increases OC cell apoptosis. Ala-scanning mutagenesis to define sequences within PTH(55-84) important for binding and bioactivity is underway. We conclude that **osteocytes** may be important targets for CPTH fragments that are secreted by the parathyroid glands or generated by peripheral metabolism of intact PTH and that accumulate in blood, especially in renal failure. Studies of functional interplay between responses to CPTHRs and (transfected)PTH1Rs, using receptor-specific ligands in OC cells, should provide new insight into PTH regulation of **osteocyte** function and survival.

L76 ANSWER 28 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002079296 EMBASE
TITLE: Cerebrovascular event, dilated cardiomyopathy, and pheochromocytoma.
AUTHOR: Dagartzikas M.I.; Sprague K.; Carter G.; Tobias J.D.
CORPORATE SOURCE: Dr. J.D. Tobias, University of Missouri, Department of Child Health, M658 Health Sciences Center, One Hospital Drive, Columbia, MO 65212, United States. Tobiasj@health.missouri.edu
SOURCE: Pediatric Emergency Care, (2002) 18/1 (33-35).
Refs: 17
ISSN: 0749-5161 CODEN: PECAE5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cerebral infarction in children may be the result of various disease processes, including emboli from intracardiac sources, paradoxical emboli from the venous system, sickle cell disease, cyanotic heart disease, vasculitis affecting the carotid or cerebral vascular system, vascular anomalies, and prothrombotic states. We present a previously healthy adolescent who presented with the acute onset of hemiparesis. Work-up revealed a dilated cardiomyopathy with a left ventricular mural thrombus as the etiology of his cerebrovascular event. Although dilated cardiomyopathy (DCM) may predispose to the development of a mural thrombus and subsequent embolic events, there are no previous reports in pediatric-aged patients of the development of an embolic event as the presenting manifestation of DCM. Further investigation of the etiology of the DCM led to the diagnosis of a pheochromocytoma. Congestive heart failure and DCM as the presenting sign of pheochromocytoma has likewise not been reported in a pediatric-aged patient. We review this unlikely sequence of events, the diagnostic evaluation of such patients, and treatment options.

L76 ANSWER 29 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001319926 EMBASE
TITLE: [Lung cancer and paraneoplastic syndromes]. CANCER DE PULMON Y SINDROMES PARANEOPLASICOS.
AUTHOR: Jurado Gamez B.; Garcia De Lucas M.D.; Gudin Rodriguez M.
CORPORATE SOURCE: B. Jurado Gamez, Avda. Villanueva Cordoba 36-1, 14400 Pozoblanco (Cordoba), Spain
SOURCE: Anales de Medicina Interna, (2001) 18/8 (440-446).
Refs: 63
ISSN: 0212-7199 CODEN: AMINEX
COUNTRY: Spain
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
037 Drug Literature Index
LANGUAGE: Spanish
SUMMARY LANGUAGE: English; Spanish

AB Paraneoplastic syndromes (PNS) are a relatively common manifestation of cancer, and in some cases they may be the first symptom. Lung cancer has the highest incidence of paraneoplastic syndrome. This fact is important considering a non explained endocrinological and neurological syndrome, it may facilitate a prompt diagnosis, and in some cases an adequate treatment. PNS evolution seems to be parallel to the subjacent cancer. PNS management requires specific measures, because in some cases, it may compromise the patient life. Neurological and endocrinological PNS associated to lung cancer are revised, and diagnosis and treatment of them are updated.

L76 ANSWER 30 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001098839 EMBASE
TITLE: Hypercalcemia after high-dose chemoradiotherapy for refractory multiple myeloma.
AUTHOR: Isshiki I.; Okamoto S.; Mori T.; Kizaki M.; Takayama N.; Watanabe R.; Ikeda Y.
CORPORATE SOURCE: S. Okamoto, Division of Haematology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan. okamoto@mc.med.keio.ac.jp
SOURCE: Hematology, (2000) 5/4 (287-292).
Refs: 12
ISSN: 1024-5340 CODEN: HMATFL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 014 Radiology
016 Cancer
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A 43-year-old man with refractory myeloma underwent allogeneic bone marrow transplantation from his HLA-matched sibling. He was conditioned with TBI (12 Gy) followed by melphalan (140 mg/m(2)). Immediately after conditioning was initiated, he began complaining of severe lumbago, and the level of serum **calcium** rose from 2.25 to 3.34 mmol/l. However, the biochemical markers for tumor-lysis syndrome such as potassium, uric acid, and lactic dehydrogenase remained unchanged. Hydration with saline and pamidronate were started, but he developed acute renal failure requiring hemodialysis for 3 weeks. His plasma **parathyroid hormone-related protein** (**PTHrP**)-NH2-terminal (3.9 pmol/l) and serum **PTHrP** -C-terminal (125.0 pmol/l) levels markedly increased immediately after conditioning. These results suggested that the increased release of **PTHrP** from myeloma cells, which resulted from destruction of myeloma cells by conditioning, was the primary contributes to the occurrence of hypercalcemia. We should be aware of the occurrence of hypercalcemia when high-dose therapy is to be given to patients with refractory myeloma.

L76 ANSWER 31 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000375327 EMBASE
TITLE: Decreased c-Src expression enhances **osteoblast** differentiation and bone formation.
AUTHOR: Marzia M.; Sims N.A.; Voit S.; Migliaccio S.; Taranta A.; Bernardini S.; Faraggiana T.; Yoneda T.; Mundy G.R.; Boyce B.F.; Baron R.; Teti A.

CORPORATE SOURCE: Dr. A. Teti, Department of Experimental Medicine, University of L'Aquila, Via Vetoio-Coppito 2, 67100 L'Aquila, Italy. teti@univaq.it
SOURCE: Journal of Cell Biology, (16 Oct 2000) 151/2 (311-320). Refs: 41
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
021 Developmental Biology and Teratology
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB c-Src deletion in mice leads to **osteopetrosis** as a result of reduced bone resorption due to an alteration of the **osteoclast**. We report that deletion/reduction of Src expression enhances **osteoblast** differentiation and bone formation, contributing to the increase in bone mass. Bone histomorphometry showed that bone formation was increased in Src null compared with wild-type mice. In vitro, alkaline phosphatase (ALP) activity and nodule mineralization were increased in primary calvarial cells and in SV40-immortalized **osteoblasts** from Src(-/-) relative to Src(+/+) mice. Src-antisense oligodeoxynucleotides (AS-src) reduced Src levels by .apprx.60% and caused a similar increase in ALP activity and nodule mineralization in primary **osteoblasts** in vitro. Reduction in cell proliferation was observed in primary and immortalized Src(-/-) **osteoblasts** and in normal **osteoblasts** incubated with the AS-src. Semiquantitative reverse transcriptase-PCR revealed upregulation of ALP, Osf2/Cbfa1 transcription factor, PTH/**PTHrP** receptor, **osteocalcin**, and pro-alpha 2(I) collagen in Src-deficient **osteoblasts**. The expression of the bone matrix protein **osteopontin** remained unchanged. Based on these results, we conclude that the reduction of Src expression not only inhibits bone resorption, but also stimulates **osteoblast** differentiation and bone formation, suggesting that the **osteogenic** cells may contribute to the development of the **osteopetrotic** phenotype in Src-deficient mice.

L76 ANSWER 32 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000028756 EMBASE
TITLE: The role of **osteoprogenitors** in vascular **calcification**.
AUTHOR: Jakoby IV M.G.; Semenkovich C.F.
CORPORATE SOURCE: C.F. Semenkovich, Washington Univ. School of Medicine, Box 8046, 660 South Euclid Avenue, St. Louis, MO 63110, United States. semenkov@im.wustl.edu
SOURCE: Current Opinion in Nephrology and Hypertension, (2000) 9/1 (11-15). Refs: 50
ISSN: 1062-4821 CODEN: CNHYEM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Calcification** is a component of vascular disease that usually occurs in concert with atheroma formation but through distinct

pathophysiological processes. Vessel wall **osteoprogenitor** cells known as **calcifying** vascular cells can form bone matrix proteins and **calcified** nodules, analogous to **osteoblastic** differentiation in bone. These cells have been isolated from the tunica media of bovine and human arteries, and both in-vitro tissue culture models and mouse models of vascular **calcification** have been established. Studies of the effects of diabetes mellitus, hyperlipidemia, estrogens and glucocorticoids on **calcifying** vascular cell function provide insight into the relationship between common human disease states and vascular **calcification**.

L76 ANSWER 33 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97382235 EMBASE
DOCUMENT NUMBER: 1997382235
TITLE: A novel cyclic adenosine monophosphate analog induces hypercalcemia via production of 1,25-dihydroxyvitamin D in patients with solid tumors.
AUTHOR: Saunders M.P.; Salisbury A.J.; O'Byrne K.J.; Long L.; Whitehouse R.M.; Talbot D.C.; Mawer E.B.; Harris A.L.
CORPORATE SOURCE: A.L. Harris, Imperial Cancer Research Fund, Medical Oncology Unit, University of Oxford, Headington, Oxford OX3 7LJ, United Kingdom
SOURCE: Journal of Clinical Endocrinology and Metabolism, (1997) 82/12 (4044-4048).
Refs: 25
ISSN: 0021-972X CODEN: JCEMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The treatment of cancer patients with conventional chemotherapy is sometimes associated with severe systemic toxicity and only a minimal survival benefit. Because of this, new less toxic and more efficacious treatments have been sought. 8-Chloro-cAMP (8-Cl-cAMP) is one of a new generation of anticancer drugs that act at the level of signal transduction. In preclinical models, 8-Cl-cAMP modulates protein kinase A (PKA) leading to growth inhibition and increased differentiation of cancer cells. 8-Cl-cAMP was given to 16 patients with advanced cancer as an infusion via an indwelling subclavian venous catheter. We showed that 8-Cl-cAMP had a parathyroid hormone-like effect leading to increased synthesis of renal 1,25- dihydroxyvitamin D [up to 14 times the baseline value, median 3.6 times; P = 0.00001 (Student's paired t test)]. This produced the dose-limiting toxicity of reversible hypercalcemia that could not be controlled by the administration of either pamidronate or dexamethasone. The treatment was otherwise well tolerated, and other cAMP-dependent pathways (cortisol and TSH) were not affected, emphasizing the marked differences between organs in their sensitivity to this cAMP analog. Our results have shown that 8-Cl-cAMP is biologically active, and it is feasible that if the hypercalcemia can be controlled, then this drug may have a role as a single agent, or as a short infusion between cycles of chemotherapy.

L76 ANSWER 34 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97318301 EMBASE
DOCUMENT NUMBER: 1997318301
TITLE: Issues concerning the role of chemotherapy and hormonal therapy of bone metastases from breast carcinoma.
AUTHOR: Harvey H.A.
CORPORATE SOURCE: Dr. H.A. Harvey, Division of Hematology-Oncology, Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17033, United States
SOURCE: Cancer, (1997) 80/8 SUPPL. (1646-1651).
Refs: 36
ISSN: 0008-543X CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A significant percentage (50-70%) of patients with metastatic breast carcinoma (MBC) will have disease involving the bony skeleton. Clonal selection mediated by **parathyroid hormone-related protein** and other factors may explain the high incidence of osseous metastases in MBC. The presence of specific growth factors and cytokines in the microenvironment of bone may contribute to the successful establishment and growth of metastatic lesions and also might determine response or resistance of these lesions to chemotherapy or hormonal therapy. **Osteolytic** bone lesions in MBC frequently give rise to serious clinical problems including bone pain, pathologic fracture, hypercalcemia, and neurologic complications. MBC often is treated with systemic chemotherapy or hormonal therapy. The purpose of this article was to review the recent published literature describing the impact of systemic chemotherapy and hormonal therapy of MBC on the response of bone lesions and their clinical course and complications. Evaluating the response of bone lesions can be problematic and may be complicated by the phenomenon of 'tumor flare' that may be observed with either chemotherapy or hormonal therapy. Use of the International Union Against Cancer criteria for the response of bone lesions is recommended. Several studies report objective responses (20-60%) of lytic bone metastases to standard combination chemotherapy regimens such as cyclophosphamide, methotrexate, and 5- fluorouracil and cyclophosphamide, doxorubicin, and 5-fluorouracil, mitoxantrone and 5-FU, newer combinations, and single agents including paclitaxel and docitaxel but responses to vinorelbine may be less frequent. Complete responses of bone lesions to chemotherapy are rare but partial responses and disease stabilization can lead to long term patient benefit. A series from the M.D. Anderson Cancer Center of patients with bone metastases treated with 5-FU, doxorubicin, and cyclophosphamide chemotherapy reported a median duration of response of 14 months. In a recent multicenter study of 195 patients with lyric lesions from MBC treated with chemotherapy, the objective response rate (complete response + partial response) in bone was 18% and 65% of the patients developed at least 1 morbid skeletal event with a median onset of 7.0 months from the start of chemotherapy. Hormone-dependent breast carcinoma has a proclivity to metastasize to bone. In earlier studies comparing aminoglutethimide or medroxyprogesterone acetate with tamoxifen, a higher response rate of bone metastases was observed for the first two agents. However, in more recent studies comparing newer aromatase inhibitors, such as anastrozole, fadrozole, and letrozole, with megestrol acetate, there were no

significant differences in rates of response in bone. Patients with MBC with bony lesions respond to both chemotherapy and hormonal therapy and can have a prolonged survival. Therefore such patients are in a more favorable position to benefit from adjunctive supportive therapy such as bisphosphonates intended to reduce skeletal morbidity.

L76 ANSWER 35 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96133807 EMBASE
DOCUMENT NUMBER: 1996133807
TITLE: Influence of dexamethasone and 1,25-dihydroxyvitamin D on Walker carcinosarcima 256 growth and **parathyroid hormone-related protein** secretion.
AUTHOR: Schilling T.; Ziegler R.; Raue F.; Cohen-Solal M.; De Vernejoul M.C.
CORPORATE SOURCE: Department of Internal Medicine I, University of Heidelberg, Bergheimerstrasse 58,D-69115 Heidelberg, Germany
SOURCE: Hormone and Metabolic Research, (1996) 28/4 (209-210). ISSN: 0018-5043 CODEN: HMMRA2
COUNTRY: Germany
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 003 Endocrinology
037 Drug Literature Index
LANGUAGE: English

L76 ANSWER 36 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96005913 EMBASE
DOCUMENT NUMBER: 1996005913
TITLE: Molecular regulation of prostaglandin synthesis: Implications for endocrine systems.
AUTHOR: Robertson R.P.
CORPORATE SOURCE: Division of Diabetes, Department of Medicine, Minnesota University Medical School,Minneapolis, MN 55455, United States
SOURCE: Trends in Endocrinology and Metabolism, (1995) 6/9-10 (293-297). ISSN: 1043-2760 CODEN: TENME4
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A wide array of prostanoids, which includes prostaglandins D2, E2, F(2.alpha.), I2, and thromboxane A2, has been known to exert regulatory effects in many endocrine systems for over 3 decades. More recently, however, molecular biological techniques have uncovered new findings that have brought about radical changes in our thinking about prostaglandin pharmacology and physiology. Two separate forms of cyclooxygenase (COX), a constitutive and an inducible form, have been identified. These two forms arise from separate genes whose expression is regulated differently. Moreover, genes for different receptor types and subtypes of prostanoid receptors have also been cloned. The various prostanoid receptor types and subtypes are coupled to transduction systems that cause alterations in intracellular **calcium** and cAMP concentrations. As importantly,

new sites of inhibitory action for corticosteroids and nonsteroidal antiinflammatory drugs in the COX-2 synthetic pathway have been uncovered that decrease COX-2 mRNA levels and enzyme mass. Most of the nonsteroidal antiinflammatory drugs are more effective in inhibiting activity of COX-1 compared with COX-2. This carries important clinical relevance, because COX-1 is proposed to play a role in normal physiologic processes rather than in mediating inflammation, which may explain the undesirable side effects of some of these drugs. Possible implications of these new developments on regulation of bone resorption as a representative endocrine system are considered.

L76 ANSWER 37 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95071653 EMBASE
DOCUMENT NUMBER: 1995071653
TITLE: Expression and secretion of **parathyroid hormone-related protein** by human bone-derived cells in vitro: Effects of glucocorticoids.
AUTHOR: Walsh C.A.; Birch M.A.; Fraser W.D.; Lawton R.; Dorgan J.; Walsh S.; Sansom D.; Beresford J.N.; Gallagher J.A.
CORPORATE SOURCE: Dept. of Human Anatomy/Cell Biology, The University, P.O. Box 147,Liverpool L69 3BX, United Kingdom
SOURCE: Journal of Bone and Mineral Research, (1995) 10/1 (17-25). ISSN: 0884-0431 CODEN: JBMREJ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We investigated the production of **parathyroid hormone-related protein** (**PTHrP**) by cells derived from explants of human bone. Using an immunoradiometric assay (IRMA), **PTHrP** was detected in conditioned medium from cultures of bone-derived cells from 6 of 7 patients investigated in this study. **PTHrP** mRNA was identified in human bone cells using reverse transcriptase-linked polymerase chain reaction (RT-PCR) and by Northern analysis. Transcripts for **PTHrP** were detected in a purified population of alkaline phosphatase positive cells isolated from human bone marrow cultures by flow cytometry, confirming the expression of **PTHrP** mRNA by cells of the **osteoblastic** lineage. Production of **PTHrP** was inhibited by 10-6 M of the glucocorticoids, prednisolone and desacetylated deflazacort, in a dose-dependent manner. In addition, RT-PCR followed by Southern blot analysis detected a decrease in steady-state **PTHrP** mRNA in cultures of human bone- derived cells treated with 10-6 M prednisolone.

L76 ANSWER 38 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92077413 EMBASE
DOCUMENT NUMBER: 1992077413
TITLE: **Parathyroid hormone-related protein** production by primary cultures of mammary epithelial cells.
AUTHOR: Ferrari S.L.; Rizzoli R.; Bonjour J.P.
CORPORATE SOURCE: Div. Clinical Pathophysiology, Department of Medicine, University Hospital,1211 Geneva 4, Switzerland
SOURCE: Journal of Cellular Physiology, (1992) 150/2 (304-311).

ISSN: 0021-9541 CODEN: JCLLAX
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
003 Endocrinology
021 Developmental Biology and Teratology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Parathyroid hormone-related protein** (**PTHrP**) plays a major role in the pathogenesis of malignant hypercalcemia, but has also been found in fetal and adult non-neoplastic tissues. Among them, lactating mammary gland was shown to produce **PTHrP**, and high levels of **PTHrP** were measured in milk. However, the regulation of **PTHrP** production. by breast cells is still unknown. Primary cultures of mammary cells isolated from rat lactating glands were grown on collagen gels in an insulin/epidermal growth factor (EGF)-supplemented medium. Under these conditions, mammary cells displayed an epithelial phenotype and their number increased more than twofold after 1 week in culture. At that time, the cells were capable of producing immunoreactive **PTHrP** (range: 25 to 150 pg/105 cells x 24 h) and PTH-like bioactivity, as indicated by a 60% increase in cyclic adenosine monophosphate (cAMP) production induced by mammary epithelial cell conditioned medium in the PTH-responsive **osteoblast**-like UMR-106 cell line. When cell proliferation was hindered by lowering plating density, by removing medium supplements, or by adding transforming growth factor (TGF)-.beta., a well-known autocrine inhibitor of mammary epithelial cell growth. **PTHrP** production was increased. In contrast, the omission of EGF or addition of specified anti-EGF antibodies decreased **PTHrP** production. In conclusion, primary cultures of mammary epithelial cells isolated from lactating rat were shown for the first time to produce **PTHrP** in vitro. This production was higher in the presence of EGF and could be modulated by cell growth rate.

L76 ANSWER 39 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 90234024 EMBASE
DOCUMENT NUMBER: 1990234024

TITLE: Removal of partial agonism from parathyroid hormone (PTH)-related protein-(7-34)NH2 by substitution of PTH amino acids at positions 10 and 11.

AUTHOR: Nutt R.F.; Caulfield M.P.; Levy J.J.; Gibbons S.W.; Rosenblatt M.; McKee R.L.
CORPORATE SOURCE: Parathyroid Hormone Laboratory, Merck Sharp Dohme Res. Lab.,West Point, PA 19486, United States

SOURCE: Endocrinology, (1990) 127/1 (491-493).
ISSN: 0013-7227 CODEN: ENDOAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **PTHrP**(7-34)NH2 and [D-TRP12]**PTHrP**(7-34)NH2 have previously been shown to be more potent antagonists than the corresponding PTH peptide, [Tyr34]bPTH(7-34)NH2. However, these peptides also display partial agonism for adenylate cyclase activity in ROS 17/2.8 cells. In this study, design of a pure potent antagonist of PTH and **PTHrP** by removal of agonism from **PTHrP**(7-34)NH2 with retention of

antagonist potency was accomplished. Since [Tyr34]bPTH(7-34)NH2 lacks agonist activity, we introduced two amino acids native to the PTH sequence into their respective positions in **PTHrP** and the potent D-Trp12 analog. [Asn10Leu11]- and [Asn10,Leu11,D-Trp12]**PTHrP**(7-34)NH2 were found to be 23- and 26-fold more potent as antagonists in ROS cells than **PTHrP**(7-34)NH2 and [D-Trp12]**PTHrP**(7-34)NH2, respectively. In addition, these peptides did not display partial agonism, even in an assay based on highly responsive cells pretreated with dexamethasone and pertussis toxin. In contrast, when the **PTHrP** sequence Asp10,Lys11 was inserted into [Tyr34]hPTH(7-34)NH2, antagonist potency declined by more than 6-fold and PTH-like agonist activity was installed. These results demonstrate that the activation domain of both PTH and **PTHrP** can be extended to include the 1-12 region and that the 10-12 region, in addition to the N-terminal hexapeptide, is important not only for receptor binding but also for hormonal signal transduction.

L10 ANSWER 1 OF 54 MEDLINE
ACCESSION NUMBER: 96079886 MEDLINE
DOCUMENT NUMBER: 96079886 PubMed ID: 7588290
TITLE: ***Regulation*** in vivo of the growth of Leydig cell tumors by antisense ribonucleic acid for ***parathyroid*** ***hormone*** - ***related*** ***peptide*** .
AUTHOR: Rabbani S A; Gladu J; Liu B; Goltzman D
CORPORATE SOURCE: Department of Medicine, McGill University, Montreal, Quebec, Canada.
SOURCE: ENDOCRINOLOGY, ***(1995 Dec)*** 136 (12) 5416-22.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951228

AB PTH-related peptide (***PTHrP***) has been shown to be the major mediator of ***hypercalcemia*** of malignancy, but may also exert effects on cell growth and differentiation. The Leydig cell tumor H-500, when implanted in Fischer rats, produces abundant ***PTHrP*** and eventually causes the death of the host animal. In the present study we have used antisense RNA technology to block the effects of ***PTHrP*** in H-500 Leydig tumor cells in vivo. The full-length rat ***PTHrP*** complementary DNA encoding amino acid -36-->141 was subcloned as an EcoRI-BglII insert in the antisense orientation into the mammalian expression vector pRc/CMV to produce the plasmid pRc-PAS. This plasmid was then stably transfected into the H-500 Leydig tumor cells with a Lipofectin reagent. After selection with the neomycin derivative G-418, a stable cell line, H-500- ***PTHrP*** -AS, was obtained which showed 80% inhibition of endogenous ***PTHrP*** messenger RNA compared to wild-type or vector-only transfected H-500 cells. Conditioned culture medium from these experimental cells showed a marked decrease in ***PTHrP*** immunoreactivity and in the ability of the medium to stimulate adenylate cyclase in UMR-106 rat osteosarcoma cells. Furthermore, inhibition of ***PTHrP*** production resulted in a significant increase in the doubling time of the H-500 cells. Transfection of the experimental plasmid into Rat-2 fibroblasts, which do not produce ***PTHrP*** , had no effect on cell growth. Control and experimental cells were then implanted sc into male Fischer rats. Animals were killed at timed intervals, and their tumor volumes were determined. Experimental animals receiving cells transfected with antisense ***PTHrP*** plasmid showed near-normal levels of plasma calcium and decreased expression of tumoral ***PTHrP*** messenger RNA. These animals also showed a 30-70% lower tumor volume during the course of the experiment compared to control animals. These studies have demonstrated that ***PTHrP*** can play a role as a promoter of tumor growth in vitro and in vivo.

L10 ANSWER 2 OF 54 MEDLINE
ACCESSION NUMBER: 95349572 MEDLINE
DOCUMENT NUMBER: 95349572 PubMed ID: 7623802
TITLE: Nucleolar localization of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** ***enhances*** survival of chondrocytes under conditions that promote apoptotic cell death.
AUTHOR: Henderson J E; Amizuka N; Warshawsky H; Biasotto D; Lanske B M; Goltzman D; Karaplis A C
CORPORATE SOURCE: Division of Endocrinology, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Quebec, Canada.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, ***(1995 Aug)*** 15 (8) 4064-75.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

similar infusions without tumor implantation. Plasma calcium, plasma levels of immunoreactive iPTHRP, and tumor ***PTHRP*** mRNA levels were determined as well as tumor size, animal body weight, and animal survival time. Non-tumor-bearing animals receiving > 50 pmol/24 h of 1,25(OH)2D3 became hypercalcemic, whereas no significant change in plasma calcium was observed in animals receiving < or = 200 pmol/24 h of EB1089. Tumor-bearing animals receiving vehicle alone or > 50 pmol/24 h of 1,25(OH)2D3 became severely hypercalcemic within 15 d. However, animals treated with low dose 1,25(OH)2D3 and all doses of EB1089 maintained near-normal or normal levels of plasma calcium for up to 4 wk. Additionally, reduced levels of tumor ***PTHRP*** mRNA and of plasma iPTHRP were observed compared with controls in both vitamin D- and EB1089-treated rats. Infusion of 50 pmol/24 h of 1,25(OH)2D3 and 200 pmol/24 h of EB1089 significantly reduced tumor volume by the end of experiment. The analogue but not 1,25(OH)2D3 substantially prolonged survival time in tumor-bearing animals with longer survival achieved at the highest dose, 400 pmol/24 h, of EB1089. These studies demonstrate that 1,25(OH)2D3 and a low calcemic vitamin D analogue are potent inhibitors of ***PTHRP*** production in vivo. Low calcemic analogues may therefore represent important alternative therapy for malignancy-associated ***hypercalcemia*** .

L10 ANSWER 19 OF 54 MEDLINE
ACCESSION NUMBER: 93131953 MEDLINE
DOCUMENT NUMBER: 93131953 PubMed ID: 8420973
TITLE: Angiotensin II ***regulates*** parathyroid hormone-related protein expression in cultured rat aortic smooth muscle cells through transcriptional and post-transcriptional mechanisms.
AUTHOR: Pirola C J; Wang H M; Kamyar A; Wu S; Enomoto H; Sharifi B; Forrester J S; Clemens T L; Fagin J A
CORPORATE SOURCE: Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California 90048.
CONTRACT NUMBER: CA 50706 (NCI)
CA 50906 (NCI)
DK 42792 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, ***(1993 Jan 25)*** 268 (3) 1987-94.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930226
Last Updated on STN: 19970203
Entered Medline: 19930218
AB Parathyroid hormone-related protein (***PTHrP***), a tumor product responsible for malignancy-associated ***hypercalcemia*** , is also produced in many normal tissues, including vascular smooth muscle cells (SMC). As ***PTHrP*** exhibits vasodilatory properties, we postulated that other vasoactive agents may control ***PTHrP*** gene expression in SMC. Addition of angiotensin II to serum-deprived SMC resulted in a marked induction of ***PTHrP*** mRNA by 2 h, with a peak (6-10-fold) at 4-6 h. Angiotensin II effects on ***PTHrP*** gene expression were inhibited by saralasin, an angiotensin II receptor antagonist, and blocked by actinomycin D and cycloheximide, suggesting a requirement for gene transcription and protein synthesis. Nuclear run-off assays revealed a 3-fold increase in ***PTHrP*** gene transcription 1 h after angiotensin II treatment. Angiotensin II also prolonged ***PTHrP*** mRNA half-life by 2-3-fold. Angiotensin-induced ***PTHrP*** mRNA is partially dependent on cyclooxygenase products and protein kinase C activation. Other vasoconstrictor substances, including serotonin and bradykinin, also stimulated ***PTHrP*** expression, whereas the vasodilator atrial natriuretic peptide did not. Addition of recombinant ***PTHrP*** -(1-141) significantly inhibited angiotensin II-induced SMC DNA synthesis. ***PTHrP*** expression is increased by angiotensin II

L10 ANSWER 13 OF 54 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94207538 EMBASE
DOCUMENT NUMBER: 1994207538
TITLE: Cytokine ***regulation*** of parathyroid hormone-related protein messenger ribonucleic acid levels in mouse spleen: Paradoxical effects of interferon- .gamma. and interleukin-4.
AUTHOR: Funk J.L.; Shigenaga J.K.; Moser A.H.; Krul E.J.T.; Strewler G.J.; Feingold K.R.; Grunfeld C.
CORPORATE SOURCE: Metabolism Section, Veterans Administration Medical Ctr., 4150 Clement Street,San Francisco, CA 94121, United States
SOURCE: Endocrinology, (1994) 135/1 (351-358).
ISSN: 0013-7227 CODEN: ENDOAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Under normal physiological conditions, PTH-related protein (***PTHrP***) is produced in a wide variety of tissues and is thought to act locally in an autocrine or paracrine fashion more analogous to cytokines than to classic hormones such as PTH. In addition, we have recently shown that, like cytokines, ***PTHrP*** is induced in the spleen during the response to sublethal doses of endotoxin [lipopolysaccharide (LPS)] an effect that is mediated by tumor necrosis factor (TNF). As complex cytokine cascades are induced in response to infectious or inflammatory stimuli, the effects of other prototypical inflammatory [interferon-.gamma. (IFN.gamma.)] or antiinflammatory [interleukin-4 (IL-4)] cytokines on ***PTHrP*** gene expression were studied. Paradoxically, IFN.gamma. (50 .mu.g), a cytokine that usually synergizes with TNF, inhibited LPS induction of splenic ***PTHrP*** messenger RNA (mRNA) levels in LPS- sensitive C3H/OuJ (OuJ) and LPS-resistant C3H/HeJ (HeJ) mice. The stimulation of splenic ***PTHrP*** mRNA levels caused by the administration of TNF.alpha. or interleukin-1.beta. was similarly inhibited by IFN.gamma., a type II interferon. In contrast, IFN.alpha. (50 .mu.g), a type I interferon, stimulated splenic levels of ***PTHrP*** mRNA. IL-4, a prototypical antiinflammatory cytokine, also had a paradoxical effect on LPS induction of splenic ***PTHrP*** mRNA levels. Instead of inhibiting LPS induction of splenic ***PTHrP*** mRNA levels in OuJ or HeJ mice, IL- 4 (200 ng) actually stimulated ***PTHrP*** mRNA levels. These complex cytokine interactions suggest that the expression of ***PTHrP*** in response to infectious or inflammatory stimuli depends on the counterbalancing effects of the specific cytokine networks induced by each stimulus.

L10 ANSWER 14 OF 54 MEDLINE
ACCESSION NUMBER: 95051075 MEDLINE
DOCUMENT NUMBER: 95051075 PubMed ID: 7962163
TITLE: Signal transduction pathways mediating parathyroid hormone ***regulation*** of osteoblastic gene expression.
AUTHOR: Partridge N C; Bloch S R; Pearman A T
CORPORATE SOURCE: Department of Pharmacological and Physiological Science, St. Louis University School of Medicine, Missouri 63104..
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, ***(1994 Jul)*** 55 (3) 321-7. Ref: 72
Journal code: 8205768. ISSN: 0730-2312.
(Investigators: Partridge N C, St Louis U Sch Med, MO)
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19950110

Schipani E; Urena P; Richards J; Bonventre J V; Potts J T Jr; +
CORPORATE SOURCE: Endocrine Unit, Massachusetts General Hospital/Harvard Medical School, Boston 02114.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, ***(1992 Apr 1)*** 89 (7) 2732-6.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M77184
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920515
Last Updated on STN: 19970203
Entered Medline: 19920506
AB Parathyroid hormone (PTH), a major regulator of mineral ion metabolism, and PTH-related peptide (***PTHrP***), which causes ***hypercalcemia*** in some cancer patients, stimulate multiple signals (cAMP, inositol phosphates, and calcium) probably by activating common receptors in bone and kidney. Using expression cloning, we have isolated a cDNA clone encoding rat bone PTH/ ***PTHrP*** receptor from rat osteosarcoma (ROS 17/2.8) cells. The rat bone PTH/ ***PTHrP*** receptor is 78% identical to the opossum kidney receptor; this identity indicates striking conservation of this receptor across distant mammalian species. Additionally, the rat bone PTH/ ***PTHrP*** receptor has significant homology to the secretin and calcitonin receptors but not to any other G protein-linked receptor. When expressed in COS cells, a single cDNA clone, expressing either rat bone or opossum kidney PTH/ ***PTHrP*** receptor, mediates PTH and ***PTHrP*** stimulation of both adenylate cyclase and phospholipase C. These properties could explain the diversity of PTH action without the need to postulate other receptor subtypes.

L10 ANSWER 28 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:314911 BIOSIS
DOCUMENT NUMBER: BR43:15636
TITLE: A PARATHYROID-RELATED PEPTIDE ***PTHRP*** ***STIMULATES*** TRANSCALTACHIA THE RAPID ***STIMULATION*** OF INTESTINAL CALCIUM TRANSPORT.
AUTHOR(S): ZHOU L-X; NEMERE I; NORMAN A W
CORPORATE SOURCE: DEP. BIOCHEM. AND BIOMED. SCI., UNIV. CALIF., RIVERSIDE, CALIF. 92521.
SOURCE: 1992 MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY (FASEB), PART II, ANAHEIM, CALIFORNIA, USA, APRIL 5-9, 1992. FASEB (FED AM SOC EXP BIOL) J, (1992) 6 (5), A1955.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L10 ANSWER 29 OF 54 MEDLINE
ACCESSION NUMBER: 93078798 MEDLINE
DOCUMENT NUMBER: 93078798 PubMed ID: 1280327
TITLE: ***Regulation*** of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHrP***) gene transcription: cell- and tissue-specific promoter utilization mediated by multiple positive and negative cis-acting DNA elements.
AUTHOR: Campos R V; Wang C; Drucker D J
CORPORATE SOURCE: Department of Medicine, University of Toronto, Ontario, Canada.
SOURCE: MOLECULAR ENDOCRINOLOGY, ***(1992 Oct)*** 6 (10) 1642-52.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States